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FIRST PRESENTATION
of the
KEYES MEMORIAL MEDAL

The ceremony of the first presentation of the Keyes Medal took place as a part of the Scientific Session of the Congress of American Physicians and Surgeons on May 10, 1933, at Washington, D. C.

On behalf of the Association, the presentation was made by Dr. William C. Quinby to Dr. Alfred Newton Richards of Philadelphia—"for contributions to the advancement of Urology."

EDWARD LAWRENCE KEYES
1843 - 1924

For each of us today as in Plato's time there is a higher as well as a lower education. . . . This higher education so much needed today is not given in the school, is not to be bought in the market place, but it has to be wrought out in each one of us for himself; it is the silent influence of character on character, and in no way more potently than in the contemplation of the lives of the great and good of the past, in no way more than in "the touch divine of noble natures gone."

WILLIAM OSLER,
1901, "Books and Men."

DR. WILLIAM C. QUINBY: We meet today to commemorate the life and work of Edward L. Keyes, a surgeon of New York City, whose energy and foresight founded in 1886 the American Association of Genito-Urinary Surgeons, and who was its first president.

Born in 1843, he received his academic training at Yale, from which he was graduated in 1863, leaving college to join the army as a captain on the staff of his father, Major General Erasmus Darwin Keyes. After a year's service during these closing months of the war Keyes entered the New York University Medical College, from which he was graduated in 1866 after the customary two years' training, with the degree of Doctor of Medicine. One of his grandfathers had been a physician—often a potent factor in determining a youngster in the choice of his career—and besides there was still ever present the war with its sorrows, its bitterness, its wastage of human life of which he had doubtless already seen aplenty. Young men were serious in those times and none more so than Keyes, who had thus decided to devote his life to bettering the lot of his fellowmen.

As a medical student Keyes must have been outstanding, for during this time he won the favorable notice of his preceptor, Dr. William H. Van Buren, the Professor of Surgery and one of the most able and popular surgeons of the city. By Van Buren's advice, after graduation, Keyes went to Paris, and it is easy to see in all his subsequent career the impress of this year spent in that scientific medical atmosphere.

Here Pasteur was actively at work and only a couple of years earlier had solved the disease of the silk worm. Claude Bernard was already famous and in this same year of 1867 Lister introduced antiseptic surgery in the famous paper published in the *Lancet*. Also in this year was held in Paris the first international medical congress. The Hôtel Dieu and the Salpétrière were replete as ever with pathology. Thus the industrious student could hardly fail to meet with daily examples long to be remembered for the profit of future patients of his own.

Returning to New York, Keyes immediately took a prominent position among his medical colleagues. By the advice of Van Buren he had devoted much of his attention to the study of dermatology while in Paris, so that naturally he sought at an early date to advance the knowledge of medicine in this field.

In November, 1869, there appears a review by Keyes on dermatology in which, after abstracting some two dozen articles from the foreign literature, the remark is made, "America has only

recently waked up to the fact that dermatology is worthy of special investigation."

Such communications reveal today merely the earnestness of a youngster intent on winning his spurs. His clearness of thought and rigid resolve to avoid all self-deception come clearly forth in his next communication to the Pathological Society in 1871 in which he relates his experience in the case of a woman suffering from an aneurysm of the mesenteric artery. It was decided to treat this by "galvano-puncture," a modality but imperfectly understood in those days. Accordingly Keyes undertook a series of experiments on dogs under ether, needling the aorta. Needles of many different compositions were tried and the conclusion reached that gold needles produced the best clot.

The patient was operated on four times—one needle being used at the first operation, two at the second, six at the third, and eleven at the fourth. The first operation lasted ten minutes. The last one an hour and five minutes. After each operation the walls of the sac became firmer, and the patient had a better appetite and less pain. Finally only one bruit could be heard over the tumor.

However, the patient gradually failed and died, and at autopsy three aneurysms were found: one of the innominate artery at its origin from the aorta, filled with firmly organized clot; the second of the aorta opposite the sixth and seventh vertebræ. Part of the contents of this was also clotted. Neither of these had been detected during life. In the abdomen lay the sac which had been treated. There was no peritonitis, but the contents of this aneurysm lacked concentric striation to indicate any special action of the needles. Keyes then makes the note that it was fortunate that the other aneurysms existed; otherwise what coagulation had occurred in the one under treatment would have been set down to galvanism. In fairness to the method, however, he called attention to the fact that the needling had done no harm and should be further investigated.

Here at the age of twenty-eight we have evidence of an honesty, industry and clarity of vision which must surely make their possessor a marked man.

And then, in 1874, appeared the immediately famous textbook, "Surgical Diseases of the Genito-Urinary Organs, including Syphi-

lis," written in collaboration with his preceptor Van Buren and later to run through many editions.

Such outstanding industry was rewarded by Keyes' appointment as Professor of Dermatology, adjunct Professor of Surgery and Visiting Surgeon to Bellevue Hospital (Medical College), and here he gave the first course of lectures in dermatology in the United States.

Soon, on the heels of all this we find Keyes making a brilliant report in 1876 at the International Congress of Medicine in Philadelphia on "the effect of small doses of mercury in modifying the number of the red blood corpuscles in syphilis." In this article, based on accurate blood counts with the aid of an instrument imported from Paris, it was clearly shown that mercury is a tonic when properly given. Salivation was no longer necessary in order to control syphilis. The accuracy of the results here reported was immediately accepted and this form of treatment generally adopted.

The art of medicine rather than its scientific side was of greater attraction to a man of Keyes' sympathetic nature, and though his graciousness and clarity of diction might make him the choice of the Academy of Medicine when it was dedicating a new home, it was in the solution of the manifold problems of the consulting room that he most truly shone. Here his earnest sympathy and unswerving morality often turned despair into hope, defeat into victory, for the patient.

This nobility of character combined with great professional skill is best brought out by an incident related by his son. "In his youth he had been isolated a month with Charles O'Connor when the latter returned from Europe with smallpox, and years after when the man who had smashed the Tweed Ring was dying at Nantucket and was told that the family had sent for Keyes, he said, 'Don't let him come; this time I want to die.' "

Alfred Newton Richards: It has been said that there are three sure signs characteristic of a genuine student: an absorbing desire to know the truth, an unswerving steadfastness in its pursuit, and an open, honest heart, free from suspicion, guile and jealousy.

These attributes you possess in full measure. Your ingenuity has overcome obstacles, let light into dark places, and made clear many uncertainties of bodily function. You are a worthy successor of your predecessors Heidenhain, Ludwig and Bowman.

Fruitful in the past, your work is also of high hope for the future.

Sir, in honoring you by the presentation of this medal commemoratory of Keyes, its founder, the American Association of Genito-Urinary Surgeons at the same time honors itself.

DR. ALFRED N. RICHARDS: Mr. President, Dr. Quinby, Members of the Congress:

I am extremely proud to be the first recipient of the medal which bears the name of this great gentleman; I am extremely proud to be permitted to carry this magnificent trophy to the University which supports me.

In accepting it, I do so as the representative of a group of my collaborators to whom the greater share of the credit for our work is due; I accept it with no illusion that what has been done in our laboratory is more than a very small part of what we now know and a very minute fraction of what we must know before we can have deep understanding of the function of the kidney. I accept it in the hope, and with some confidence in the hope, that we now possess some methods with which it may be possible to reinforce or correct with demonstrable facts some of our current hypotheses concerning the functions of the renal tubule. And, finally, I accept it with recognition of its implicit obligation to work with as much industry and speed as is consistent with sound observation in order to place in the hands of the clinician information of true usefulness in his indispensable service to man.

I beg of Dr. Quinby to convey my humble and profoundly appreciative thanks to the Association which he represents and to which I am so deeply indebted.

THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

FIRST DAY, MAY 8, 1933

BILATERAL LIPOMAS OF THE TUNICA VAGINALIS

CLYDE LEROY DEMING, M.D.

From the Department of Surgery, Yale University and the New Haven Hospital, New Haven, Connecticut

Up to date thirty-two authentic tumors of the tunica vaginalis propria have been reported. Thirteen of these were fibromas, twelve sarcomas, two adenomas, two rhabdomyomas and one each of lipoma, osteochondroma and lymphangio-endothelioma. In addition, other tumors have been accredited to the tunica vaginalis, but on account of their size the exact site of their origin could not be definitely ascertained. The difficulties encountered are exemplified in the presentations of Klebs, Kocher, Orth, Roeder, Minet, Grote and Rubaschow.

In this paper attention is called to tumors of the tunica vaginalis propria composed of adipose tissue. The only such authentic tumor is that described by Park (1886). Lipomas of the cord, too, are rare, according to Schiller. He ascribes their origin to the small globules of adipose tissue in the tunica vaginalis communis. These must not be confused with the properitoneal lipomas. A single lipoma of the epididymis (Wildbolz) and three authentic lipomas of the testicle (Roeder) have been reported. Lipomas of the scrotum have been discussed by Cecil in 1927.

The case to be presented is unique from both pathologic and clinical points of view.

CASE REPORT

Mr. E. K., thirty-four years old, a school teacher (No. A-5611), entered the New Haven Hospital November 17, 1931, complaining of swollen testicles. The family history is not pertinent except that he has been married for three years and does not have any children. He

stated that he had enjoyed good health. As a child he had mumps, measles, chickenpox and diphtheria without complications. His tonsils were removed at the age of fourteen. He contracted gonorrheal urethritis at the age of eighteen, was treated by a physician and discharged as cured in four weeks without complications. His present illness began about October 1, 1931. While riding in an automobile, he experienced a slight pain in the right testicle and noticed that night a slight swelling of his testicles. The pain persisted and became dull and aching. He continued work for one month, at which time he decided to stop on account of the discomfort. For the month prior to admis-

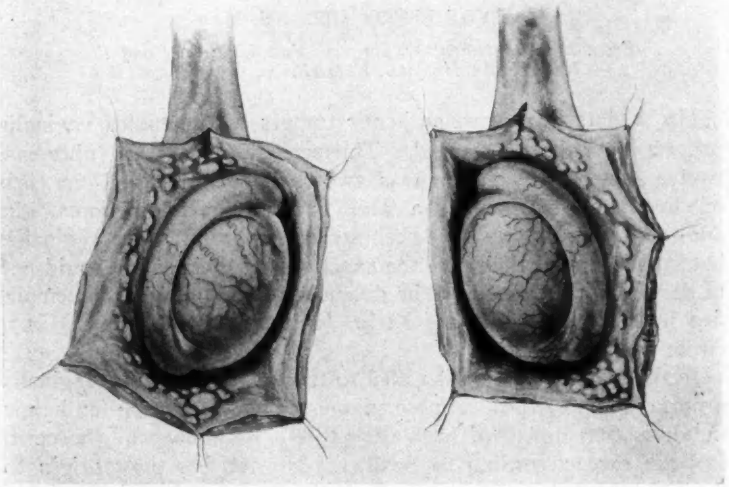

Fig. 1. Photograph of drawing showing right and left tunica vaginalis opened, each with its chain of adipose nodules extending a short distance from the convex border of the epididymis.

sion, he wore a suspensory without relief. He did not have any urinary disturbances. His sexual life was normal and he could not recall any injury to the scrotum.

On examination the patient appeared well developed and nourished. The skin and scleræ were clear. The systolic blood pressure was 120; the diastolic 75 mm., pulse 80; respiration 20 and temperature 98° F. The eyes were normal without evidence of exophthalmos. The tongue, teeth, gums and pharynx were normal. The thyroid gland was enlarged to about one and a half times normal size. No changes were noted in the chest and abdomen. The penis was normal. There was no

discharge from the urethra. The scrotum appeared normal, but on palpation a chain of nodules was felt beginning at the lower pole of each testicle and extending upward along the course of each epididymis. These nodules varied from shot to pea size and were larger at the poles. They were slightly tender, hard, and appeared to be attached to each epididymis. The testicles, vasa and cords were normal. Nothing unusual was noted on rectal palpation. The extremities and their reflexes were normal.

The red blood cells were 5,300,000 with a hemoglobin of 102; a

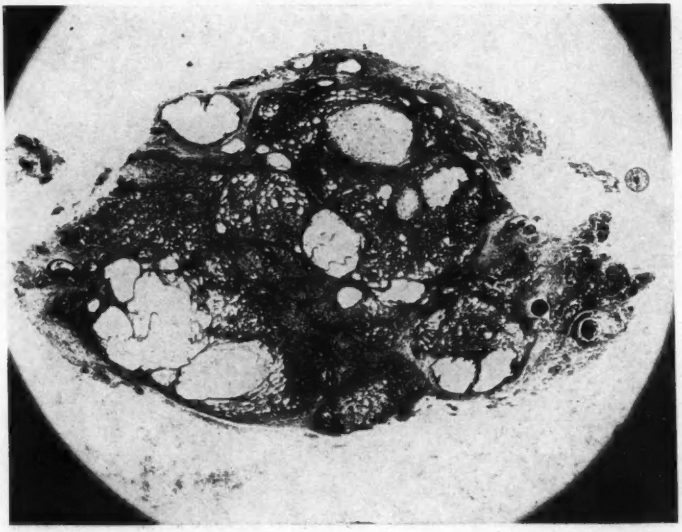

Fig. 2. Photomicrograph (× 12) of one of the nodules, showing adipose tissue. Large and small spaces are to be noted containing necrotic material.

white blood count of 5,200 with 64 per cent polymorphs and 36 per cent lymphocytes. The urine was yellow, clear, acid, sp. gr. 1.016 with a slight trace of albumin, no sugar, very rare red blood cell, no casts, pus or organisms. The Wassermann and Kahn reactions of the blood were negative. The basal metabolism test was minus four.

The pre-operative diagnosis was bilateral tuberculous epididymitis.

On November 18, 1931, each testicle in turn was delivered through an inguinal incision. On opening each tunica vaginalis the corresponding epididymis and testicle appeared to be normal. On the parietal

portion of each tunica vaginalis a chain of yellow, white, nodules varying from 1 to 5 millimeters in diameter projected into the cavity. The right epididymis was removed together with the tunica vaginalis. On the left side a strip of the tunica vaginalis with the small nodules was excised. The wounds, closed without drainage, healed without complications.

The patient was discharged, relieved, on the thirteenth day and had no recurrence when last seen on March 14, 1933.

The gross specimen consisted of a right epididymis with a portion of the vas and a thin elastic piece of tissue. The surface of the epididymis

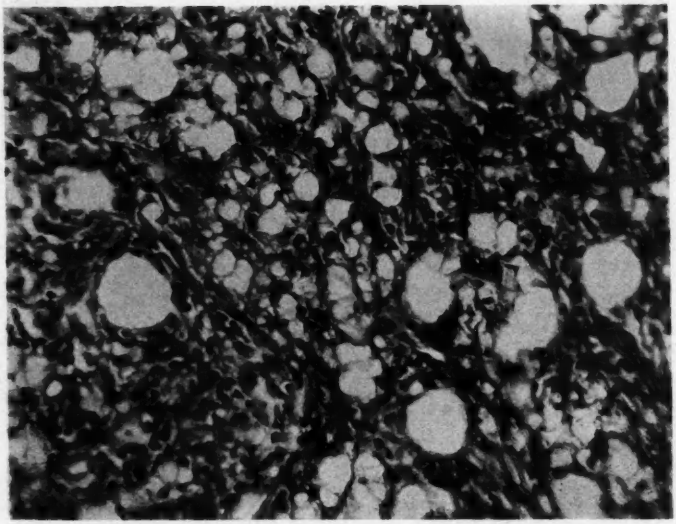

Fig. 3. Photomicrograph (× 125) showing the adipose tissue, fat spaces, lymph spaces and occasional giant cell.

appeared smooth and glistening. To the epididymis a thin membrane was attached, the inner surface of which, too, was smooth and glistening except for a series of elevated yellow nodules having a similar glistening surface. These nodules, about thirty in number, varied from 2 to 7 millimeters in diameter and were situated in a row along the convex surface of the epididymis about 3 to 5 millimeters from the line of reflexion. At both ends of the row the nodules were larger and more numerous. The surface of the individual nodules appeared slightly lobulated. On cut section some of the nodules had a yellowish white appearance; from others, a thick yellow fluid exuded. The

epididymis and vas appeared normal. The other piece of tissue consisted of a thin membrane with one glistening surface showing nodules similar in size and arrangement to those described in the membrane attached to the epididymis.

Miscroscopic preparations showed the nodules to be composed mainly of adipose tissue of the embryonal type. Blood vessels were rather numerous and many were surrounded by a collar of small round cells. Streaks of hyalinizing fibrous connective tissue formed incomplete septa. There were a number of large and small round spaces, empty or containing a scant network of light pink staining material. Some communicated with one another and appeared to be surrounded by a thin fibrous connective tissue capsule. Smaller clear spaces twice to twenty times the size of an adipose tissue cell were numerous. In occasional areas an amorphous pink staining material was surrounded by large, elongated cells. An occasional giant cell might also be seen. Preparations from the epidymis showed occasional foci of small round-cell infiltration in the intertubular connective tissue, while those of the vas deferens appeared normal. Staining with Sudan iii showed the tissues heavily impregnated with fat.

Diagnosis—multiple foci of aberrant adipose tissue in the tunica vaginalis propria with necrosis and chronic inflammatory reaction.

A chemical analysis of some of these nodules (by Professor Frank P. Underhill) showed them to contain fat, saponified fat and calcium.

Some of the microscopic slides were sent to Dr. J. Ewing, who made the following comment: "There are many large and small spaces in the fat tissue which seem to be lymph spaces. One might assume that the tumor is primarily a lipoma with secondary dilatation of the lymph spaces. Or, the spaces may represent oil cysts, but this is unlikely because the spaces are empty. The general structure resembles lymphangioma. One might compromise and call it lymphangio-lipoma."

The question arises whether these symmetrically placed, multiple nodules of adipose tissue are to be regarded as misplaced remnants of retroperitoneal adipose tissue or are real neoplasms. While the structure appears to support the latter view, the multiplicity and the symmetrical arrangement of the nodules speak against it. Again the degenerative changes, occurring without any story of trauma, may have been present and have been the cause of the clinical manifestations; but at the time of its occurrence it was too slight to make an impression. Whether the nodules are to be regarded as true neoplasms, that is lipomas, or not, is a matter of opinion. I am inclined to believe that they are lipomas.

The author wishes to express his gratitude to Dr. James Ewing of New York and Dr. Bela Halpert of New Haven, whose valuable aid is appreciated.

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PYO-URACHUS

WITH REPORT OF A CASE

ALEXANDER R. STEVENS, M.D.

From the Urological Service of Bellevue Hospital, New York City

On the basis of embryologic research, objections might be raised to the correctness of the title of this paper, if one examined the gross specimen alone. But I think the evidence offered by the microscope will justify the diagnosis.

The earlier notion that the urachus developed from the allantois was abandoned some years ago, when the bladder was established as its origin, according to Felix.[4] In fetal life, the upper part of the bladder (which is derived from the ventral cloaca) becomes narrow and tubular, and is known as the urachus. "At birth the urachus reaches the umbilicus and is attached at its apex by three fibrous strands, one to each umbilical artery and one passing into the umbilical cord. The last is the only remnant of the allantois. Immediately following birth the bladder begins its descent, taking the urachus with it" (quoted from Begg[1]). In the adult, the urachus is said to be usually not over 5 cm. long and accordingly its upper end is usually 10 to 12 cm. below the umbilicus. But one logically infers that in the adult the urachus *may* extend much higher. Begg apparently explains most midline infections found in the space just below the umbilicus, and between the peritoneum and the transversalis fascia, as due to the escape of urine through minute ruptures in the wall of the urachus. This urine enters the space above, occupied by the so-called Luschka's plexus, and bounded on each side by the obliterated umbilical arteries.

Cullen[2] describes the urachus in the adult as a fibrous cord, which may be patent at certain points; while the studies of Begg indicate that normally it never loses its epithelial coat, although the canal may be blocked here and there by proliferation or desquamation of epithelium. Nevertheless, rounded structures, varying in size from smallest beads to large cysts holding many liters, and tubular dilatations are sometimes found.

Most inflammatory conditions encountered in this region extend

down to and are closely attached to the bladder; they may, but usually do not, reach up to the umbilicus. It is also true that a patency exists at either the umbilical or the bladder end, or both, in the majority of cases reported. Cullen, in his exhaustive search of the literature, found and summarized only about a dozen cases of abscess in the region of the urachus with apparently no opening at either end.

These abscesses are sometimes incised and drained, and are better so treated if large. The smaller ones with a thick fibrous coat are

Fig. 1. Posterior view showing adherent peritoneum removed with the mass, which was 14 cm. long. The umbilicus is at the large end; the middle strand at smaller end was attached to the bladder.

often excised without great trouble or risk. The danger of rupture into the peritoneal cavity is a real one. Danneen and Margold[8] have recently reported an instance of general peritonitis from this cause. And Squier and Cahill[5] found small abscesses within the peritoneum, but walled off by omentum, in one of the three cases of chronic urachal infection which they have reported.

CASE REPORT

A negro, twenty-four years of age, entered Bellevue Hospital, January 31, 1933, complaining of an aching pain about the umbilicus.

Family History.—Irrelevant.

Past History.—He had never had any serious illness nor any operation. General health was excellent. He had had gonorrhea in 1931, and had contracted the same disease again, three weeks before admis-

sion. This was evidently mild in character. There was no urinary frequency nor gross hematuria.

Present Illness.—Without noting any sudden onset, the patient had been complaining of pain, aching in character, about the umbilicus, for about one week. There was no nausea or vomiting. The bowels were regular, but Epsom salts were taken, hoping for, but without obtaining, relief from pain. There was neither history nor evidence of any infection, except the urethritis and the abdominal condition.

Examination.—The routine physical examination of the head, neck and chest was negative. The upper abdomen was quite normal. The liver, spleen and kidneys were not felt. In the midline below the um-

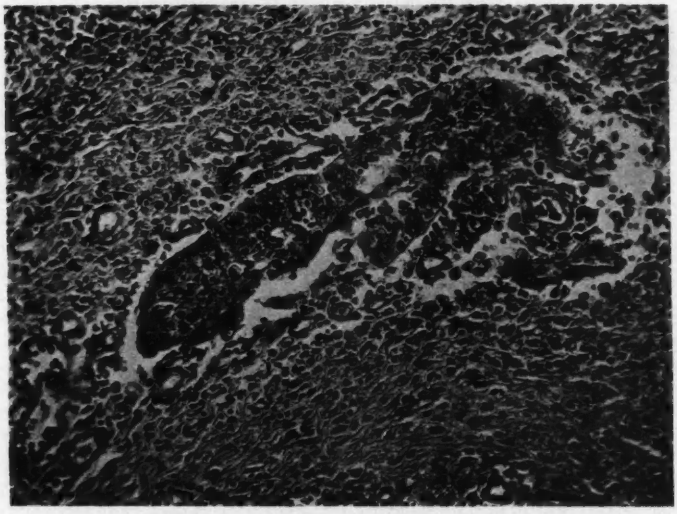

Fig. 2. Section through thick mass, showing central pocket of pus with an island of epithelium, surrounded by a ring of smooth muscle.

bilicus was moderate tenderness on fairly deep pressure; one could feel a mass within or near the anterior abdominal wall, apparently about 3 cm. in width, and extending downward from the umbilicus 6 cm. or more. The umbilicus was clean and dry. There was no distention of the abdomen, no rebound tenderness, no rigidity, but some resistance to deep palpation.

There was present a slight urethral discharge which contained Gram-negative, intracellular diplococci. The scrotal contents were normal, and the prostate was recorded as "slightly enlarged and tender, with

acute prostatitis of the right lobe." Extremities and reflexes were normal.

The urine contained a little albumin, no sugar, no pus except in the shreds, but a number of red blood cells; the same was found before operation and five days afterwards, but the urine was normal on the twelfth day after operation. The Wassermann test was negative on two examinations. The blood N.P.N. was 28.0 mgms. per 100 c.c., and

Fig. 3. Section through tail, near thick mass, showing a mass of smooth muscle surrounded by vascular connective tissue, and containing a central hyalinized area with possible small lumen but with no epithelium.

creatinin 1.6. Leukocytes the day before operation were 17,200 with 84 per cent of polymorphonuclear cells.

Cystoscopy was not done. It was felt that the red blood cells in the urine were likely caused by the sub-acute gonorrheal prostatic condition.

A diagnosis of inflammation of the urachus was made.

Operation.—On February 2, under spinal anesthesia with nupercain, a midline suprapubic incision was made from umbilicus to pubis. After separating the recti muscles, the mass was easily felt, and was dissected

free on both sides; it was intimately attached to the umbilicus above, but became a small fibrous cord at its lower end. The latter was about 6 cm. long and was firmly attached to the bladder.

The peritoneum was adherent on the posterior aspect of the large mass, and was incised at one side. Omentum was adherent but easily freed. The appendix with old adhesions at its base came into view and was removed. The inflamed mass was then removed with the umbilicus above and the fibrous strand at its lower end which was cut off near the bladder. Two other fibrous strands running off into the abdominal wall on either side, and believed to be the obliterated umbilical arteries, were also cut between ligatures. The edges of the wound came together easily, and it was closed without drainage.

The convalescence was entirely uneventful and the patient went home on February 18 with the operative wound healed.

In the pathologic report (by Dr. Douglas Symmers, director of laboratories, Bellevue Hospital) which follows, the description of the sclerotic appendix is omitted.

Macroscopic Examination.—Inflammatory mass measuring 8 cm. in length, and averaging over 2 cm. in diameter was found. Superiorly, the umbilicus was attached; inferiorly, there were three processes, each about 5 cm. long, the lateral two of which were probably obliterated umbilical arteries. On longitudinal section through the inflammatory mass, there was found a spindle-shaped cavity 4 cm. long and about 5 mm. in its greatest diameter, filled with pus. The wall of the cavity was firm and 9 mm. in thickness.

Microscopic Examination.—Sections taken at three different levels of the large inflammatory mass showed essentially the same pictures, namely an outer layer of connective tissue representing a chronic productive inflammatory lesion, then a circular layer of bundles of smooth muscle. Within this was a collection of polynuclear leukocytes together with islands of epithelium of the transitional cell type.

Sections cut at nine different levels through the tail-like process inferiorly, showed collections of smooth muscle fibers cut transversely, and connective tissue. In those sections taken near the large mass, there was seen, in the immediate center of the area of smooth muscle, a tube-like mass of pinkish staining, hyalinized, poorly nucleated material, representing apparently altered muscle tissue. Within this pinkish material was a small crescentic space which might represent a lumen. But in the sections taken nearer the bladder end of the process there was no hyalinized material and no indication of a lumen. There was no epithelium found in any of the nine sections made through this process.

In résumé, we had an elongated inflammatory mass, firmly attached above at the umbilicus, and connected below with the bladder by a stout cord. Cross sections through the large mass showed

a central cavity filled with pus and containing islands of epithelium; this was surrounded by a continuous ring of smooth muscle and an outer layer of connective tissue—a picture strongly resembling the structure of the bladder wall.

The cord-like structure below the larger mass contained smooth muscle and fibrous tissue with no epithelium found anywhere and not even a suggestion of a lumen in its lower portion.

The origin of the infection was not clear. The close attachment to the umbilicus suggested this as the source, yet superficially the umbilicus was clean. A hematogenous infection from the prostate or some unknown focus is possible, but it seems hardly plausible to suppose the bladder to have been the source of infection in this case.

CONCLUSION

The case of pyo-urachus reported differs from most instances of inflammation of the urachus in that:

1. There was no opening leading to the umbilicus or to the bladder.
2. The urachus had not retracted downward as usual, but still remained attached to the umbilicus in adult life.
3. The urachus had remained patent at its upper portion as proved by the islands of epithelium found.
4. The urachus, therefore, had apparently become merely a cord of smooth muscle and fibrous tissue at the lower end, with no sign of epithelium nor of a lumen.
5. The inflammation was confined to the upper part of the urachal structure, with no involvement of the bladder end.

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SPONTANEOUS VESICAL FISTULÆ IN URINARY TUBERCULOSIS

HENRY O. MERTZ, M.D.

Department of Urology, Indiana University School of Medicine, Indianapolis, Indiana

A spontaneous bladder fistula is rare. It develops without trauma or extravesical force, because of a diseased bladder wall. The perforation results from extension from without as from bowel, rectum, vagina, uterus, et cetera, or, less frequently, because of primary disease in the bladder wall itself; trophic changes, new growths, simple ulcerations, syphilis or tuberculosis. This discussion is limited to spontaneous perforation of the bladder wall, the result of a vesical tuberculosis, and the study is based upon the clinical observation of a vesico-vaginal fistula developing during the course of a urinary tuberculosis in a child.

CASE REPORT

E. M. S., aged thirteen, entered the James Whitcomb Riley Hospital for Children on May 13, 1930, complaining of constant leakage of urine for the past six years, with steady loss of health.

The following history was given by Dr. J. R. Dillinger of French Lick, Indiana. The child as a babe and until five years of age was said to be normal. She had had measles, and whooping cough without complications. Between her fourth and fifth year she developed a bladder frequency which, while more or less constant, did not become really troublesome until she was about seven years of age, when it grew more marked. From this time, although there were periods of slight remission, the general course of her bladder trouble was a progressive one, and she gradually grew intermittently incontinent, and when eleven years old developed complete incontinence without further desire to void naturally.

When she entered the hospital she was constantly wet, and was gradually losing strength. Examination of the head, neck, and chest was negative. The urine was purulent and stains for tubercle bacilli were negative. There was no animal inoculation of the urine made. The two-hour phthalein output was 60 per cent. Mantoux test was positive. Blood Wassermann test made on two occasions was negative. X-ray of the urinary tract was negative for stone and the kidney shadows were not well shown. There was bilateral coxa valga.

The patient's father and mother were both living and well. There were two brothers and one sister living and well. There was no history of syphilis and no history of tuberculosis contact.

Upon attempting cystoscopy the Butterfield cystoscope could not be

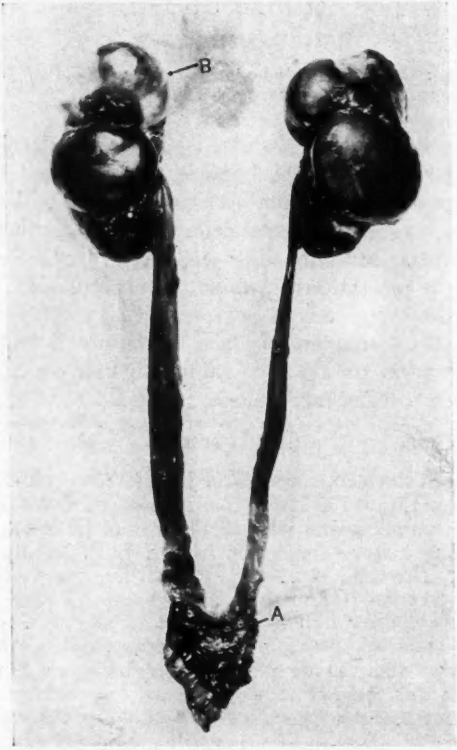

Fig. 1. Photograph of kidneys, ureter and bladder immediately after removal at autopsy. The fistulous opening is at *a*. Both kidneys were lobulated. The upper pole of the right kidney contained a cyst, *b*. The entire bladder is shown in this illustration indicating its small size.

introduced into the bladder sufficiently far for examination. The instrument was obstructed with the lens system still in the urethra. This could not be overcome and any attempt gave the patient rather severe pain and resulted in some bleeding. There was no urethral obstruction.

The bladder capacity could not be determined, as fluid introduced through a catheter was immediately expelled through the vagina.

Under inhalation anesthesia, rectal and vaginal examinations seemed to disclose a definite nodular, fixed mass high up on the base of the bladder region slightly to the left of the midline and apparently extending upward on to the posterior wall of the bladder. The entire roof of the vagina high up was indurated, rough and fixed, but the vesico-vaginal opening could not be definitely located.

A consultation with the general surgical staff was secured and the above physical findings were corroborated.

The patient was observed for three weeks, during which time there was a gradual decline and on June 5, 1930, a midline suprapubic incision was made. No bladder was found at its usual location and the peritoneum was opened. The uterus and tubes appeared normal. There was a diffuse inflammatory mass encountered on the anterior surface of the uterine body extending well down under the pubic bone, which proved to be perivesical inflammatory tissue. This was very adherent and in our manipulations the bladder was torn into. The bladder was about 1¼ inches in width and 1 inch in anteposterior diameter with a capacity estimated at not more than 5 to 8 c.c. The bladder wall was soft. The ureters were dilated and their walls thickened, and the kidneys were found enlarged and lobulated. An attempt to do an ureteral transplant into the rectum was considered inadvisable. The peritoneum was closed and the bladder wall was closed about a small rubber catheter as best we could.

The opening of the vesico-vaginal fistula was just back of the trigone and was about 0.5 cm. in size (Fig. 1, *a*).

The patient returned to her room in fair condition and other than a troublesome nausea for forty-eight hours her convalescence was satisfactory until the eleventh day postoperative, when she suddenly grew worse and died within a few hours. Her postoperative temperature had never exceeded 100.

SUMMARY OF POST-MORTEM EXAMINATION*

Externally the body was emaciated, although development appeared to be normal for a female in the twelfth year. A midline linear surgical incision approximately 5 cm. in length from which could be expressed turbid urine extended upward above the symphysis pubis.

There was moderate dilatation of the chambers of the right heart and the myocardium, which did not resist perforation to the usual degree, showed marked parenchymatous degeneration. Neither gross nor microscopic evidence of pulmonary tuberculosis was found. The omentum was attached by thin avascular adhesions to the structures surrounding the operative wound and to the adjacent pelvic organs. In

*The post-mortem and tissue examinations were done by Dr. W. Dodds, Pathologist, Indiana University School of Medicine.

the peritoneum on the under surface of the diaphragm overlying the left lobe of the liver were numerous tubercles, many with caseous centers, varying in size from 1 or 2 millimeters to 4 or 5 millimeters in diameter. Histologically these lesions presented the picture of an active tuberculosis. Gross evidence of tuberculosis of the mesenteric and retroperitoneal lymph nodes was lacking.

The urinary bladder into which the suprapubic wound was found to lead was a small, moderately thin walled structure with an estimated

Fig. 2 *(left)*. Photograph after fixed for mounting. The arrow points to the opening of the fistula.
Fig. 3 *(right)*. Sections taken from *b* for microscopic study.

capacity of 4 to 5 cubic centimeters. The ureteral orifices were narrow but patent. In the posterior wall of the bladder, just beyond the left ureteral orifice, was a ragged opening 5 millimeters in diameter leading into a fistulous tract to the vagina (Figs. 1 and 2, *a*). The margins of the tract were necrotic and the mucosa of the bladder was absent. In its mid-portion the left ureter measured 11 millimeters, and the right 15 millimeters, in diameter. The left ureter at the uretero-pelvic juncture narrowed to a diameter of 2 millimeters. This resulted from cicatrization of scar in its wall. Both kidneys were moderately enlarged and their pelves moderately dilated. At the upper pole of the right kidney was a large cyst measuring 3 centimeters in diameter (Fig. 1, *b*, and Fig. 3, *a*).

At post-mortem it was believed the small size of the bladder represented a congenital hypoplasia of this structure, and that the dilatation

of the ureters had resulted therefrom. The kidneys were not sectioned at this time and the entire specimen consisting of kidneys, ureters, bladder and vagina were prepared for museum mounting. However, when the kidneys were later sectioned the following additional facts were discovered.

The mucous membrane of the left renal pelvis was greenish brown in color and covered with necrotic debris. Small tubercles were seen

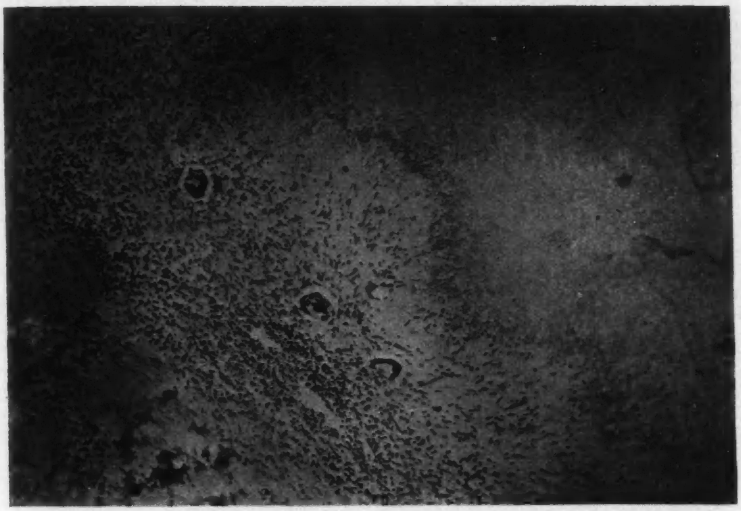

Fig. 4. Low power microphotograph. Marked caseation with marginal tubercles.

in the mucosa of the major and minor calices. At the lower pole of this kidney there was extensive ulceration of the mucosa with large areas of caseation necrosis involving the kidney parenchyma and eroding approximately one-half of the renal cortex at this pole of the kidney. In the posterior portion was a caseous tubercle 1 centimeter in diameter, which had destroyed almost an entire renal pyramid with the corresponding cortex, but which had not eroded the lower major calix in relation to which it was found (Fig. 3, *b*).

The mucosa of the right renal pelvis presented the same features as that of the left, except that the tubercles were more numerous and there was more widespread ulceration and caseation necrosis extending deeply into the kidney parenchyma. The upper pole of this kidney was represented by a cyst which contained clear yellowish fluid. The internal configuration suggested that it represented the major calyx

with its appended minor calices which had become detached from the remainder of the renal pelvis by the cicatrization of scar. The renal parenchyma at this pole of the kidney was almost completely atrophied.

The mucous membrane of both ureters was found to be hyperemic and contained numerous small tubercles which became more numerous toward their upper ends. Microsection of the caseous areas in the left kidney revealed characteristic lesions of active tuberculosis. Typical

Fig. 5. High power microphotograph. Langhans' giant cell with surrounding epithelioid cells.

tubercles, many of which contained cells of Langhans type, were in evidence. Acid-fast stains of this tissue did not reveal acid-fast bacilli. The superficial tissues at the margin of the fistulous tract in the bladder wall were necrotic and contained an abundant infiltration of inflammatory cells. Numerous inflammatory cells of the mononuclear type in the underlying tissues indicated a chronic inflammatory process but no tubercles were seen. Histologic study of the cyst in the right kidney showed it to be lined with transitional epithelium but no evidence of active tuberculosis could be found.

A microscopic section, taken through the posterior bladder wall, with the adjacent wall of the vagina, failed to reveal evidence of active tuberculosis. Small round-cell infiltration of the bladder musculature, which was much of intact, was indicative of a chronic inflammatory process.

The most significant lesion found post-mortem was the bilateral renal tuberculosis, although Mycobacterium tuberculosis was not found either ante-mortem or post-mortem. When the nature of the renal pathology was discovered an attempt was made to establish relationship between the renal tuberculosis and the vesicovaginal fistula. Unfortunately, microscopic examination failed to establish this relationship. It is possible that the severe necrotizing inflammation of the bladder may have masked the characteristic tuberculous lesions. The location of the fistula at the mouth of the left ureteral orifice suggests strongly that an ulcer developed at this point as a result of the discharge of urine containing tubercle bacilli from this ureter.

The small size of the urinary bladder is interpreted as resulting from an atrophy of disuse following the establishment of the vesicovaginal fistula. The route traversed by the tubercle bacillus in reaching the kidneys is not clear from the observed data. It is probable that a minute histologic examination of the mesenteric and retroperitoneal lymph nodes might have disclosed the source of the tubercle bacilli.

It seems most probable the immediate cause of death was failure of the myocardium, as this structure exhibited both gross and microscopic evidence of severe damage.

COMMENT

The urinary symptoms developed at the age of five. At autopsy, eight years later, there was a striking absence of the disease beyond the urinary tract, a single area on the diaphragm being the only other tuberculous lesion found. A bilateral surgical renal tuberculosis was present, the kidney changes evidencing nature's efforts in resisting the infection. The perivesical inflammatory reaction was marked, and these tissues were very adherent to the bladder. Tuberculosis in a child is usually massive and progresses rapidly, and when urinary it is seldom surgical, and rarely will there be the degree of resistance to the disease as here displayed.

The bladder was no larger than the terminal phalanx of the thumb. Its capacity was very reduced. At operation its walls were fragile and easily torn. Pathologic examination showed the mucosa absent, with the muscularis much intact. This does not conform to the end-results of a vesical tuberculosis as ordinarily observed; that the unusual termination was the result of the establishment of the vesico-vaginal fistula is evident, but that such drainage need not be followed by so marked decrease in the bladder capacity is common observation. We have never encountered it in any instance in which we have surgically established vesico-vaginal drainage as a therapeutic measure in a vesical tuberculosis. Halle

and Motz report five such bladders drained surgically and indicate the unusual interest in their development. In their cases they found the tuberculous lesions to have been extensive and superficial, with the deeper structures showing an ordinary interstitial cystitis. Heiter reports a similar bladder in a patient who had developed a spontaneous vesico-vaginal fistula. He had difficulty in isolating the bladder because of its small size. In such bladders the pericystitis is marked and the tissues very adherent to the bladder wall.

Notwithstanding the rather thickened bladder wall, the bladder was easily torn into at the operation and the margins were with difficulty coapted. Pathologists have observed, associated even with the greatly thickened, indurated, bladder walls of advanced vesical tuberculosis, localized areas of softening extending through the wall to the prevesical tissues, rendering the bladder easily torn and penetrated at these points. These no doubt represent pyogenic invasions of the bladder wall, and are distinct in their action from the tuberculous process.

DISCUSSION

The writer has collected from the literature twenty-nine cases of spontaneous perforation of the bladder wall by a tuberculous ulcer. Of these, eleven were clinical studies, fourteen were autopsy findings, with the record of four being insufficient to judge their source. References to other similar cases were found without sufficient information being given to prove of value here. Reports of simple ulcers perforating the bladder wall, the diagnosis being based upon the absence of tubercle bacilli and giant cells in the bladder ulcer, appear in the literature, with insufficient information to justify eliminating a urinary tuberculosis. This negative pathologic information can not be admitted as final, and it is not improbable certain reports of spontaneous perforation of simple ulcer are really tuberculous ulcers. Again, two diseases may coexist, either of which could produce the fistula. This was true in the following observation of the writer: A colored woman, aged 34, had developed a spontaneous vesico-vaginal fistula. There were tubercle bacilli in her urine and a Wassermann test showed four plus. After the fistula was well established, there was a continued destruction of tissues at the base of the bladder. The patient subsequently died of a pulmonary tuberculosis. An autopsy

was not secured. Both tuberculosis and syphilis may have contributed to the vesico-vaginal lesion.

The unreliability of a negative pathologic report of the bladder wall in eliminating a vesical tuberculosis is emphasized by Schürer. His patient had pulmonary tuberculosis, renal tuberculosis, the perforation into the peritoneal cavity of an ulcer previously diagnosed at cystoscopy as a tuberculous ulcer, and a tuberculous peritonitis following perforation. Neither tubercle bacilli nor giant cells were found in the ulcer removed at operation nor in the bladder wall subsequently secured at autopsy. This was also true in Laffitte's case. Alton found both tubercle bacilli and giant cells in the bladder wall of his patient. Halle and Motz, and Walker, from their studies of tuberculosis of the bladder, indicate that in the destructive stages tubercle bacilli or tubercles may or may not be found in the tissues.

Why occasionally a tuberculous ulcer will perforate the bladder is not clear. Usually tuberculosis of the bladder gives rise to ulcerations involving the submucosa most frequently, the deeper bladder muscle more rarely, with varying degrees of fibrotic changes in the bladder wall, resulting in a rigid, thick-walled cavity of restricted capacity and impaired function. In the development of the disease the defensive, reparative forces are sufficient to wall off and limit the process to the bladder alone. Very rarely, however, this does not occur, and the destructive process continues until the ulcer penetrates the bladder wall. It is suggested this unusual action may be the result of a tubercle bacillus of greater virulence;* an innate low resistance of the tissue to the disease; a symbiotic action of certain mixed infections unusually virulent, or to the presence of microbic embolic lesions of the small vessels in the region of the ulcer. Certain observers have concluded that perforation results from the mixed infection in the bladder wall, and the actual penetration is due more to the pyogenic invasion than to the specific action of the tubercle bacillus. The resistance of individuals to tuberculosis differs widely, and the development of a vesical fistula complicating a urinary tuberculosis is probably not to be explained on any one cause, but will vary with individual patients.

*Bernard and Salomon suggested the tubercle bacilli developed dual toxins, one necrosing and one sclerosing in its effect on tissues, and that these may vary in relative amounts in different strains of tubercle bacilli. J. de Physio. et de Path. Gen., 1905, 7:303.

In twelve of the cases the perforation was in the vertex of the bladder, and in thirteen, in the base. These figures probably do not give an accurate idea of the relative frequency of the location of the perforation, as those instances where the ulcer perforates into the prevesical space or the peritoneal cavity will be given greater prominence in the literature. Probably the greater majority perforate the base of the bladder. Of the twelve perforating the upper wall of the bladder, one-half (all clinically diagnosed cases) opened into the peritoneum. Of the remaining six draining into the perivesical space, three were clinical findings. Six of the ulcers penetrating the base of the bladder were clinical observations, of which five opened into the vagina and one into the rectum.

The perforation occurs most frequently by a single orifice in the center of the necrotic area. There may be multiple openings pinhead in size (Schürer), or a single orifice sufficiently large to admit two fingers (Stutzen). Two widely separated perforations may be present in the same bladder. In Hewitt's case, one perforation opened into the prevesical space and a second into the rectum. The perforating ulcer may be small or involve a large segment of the bladder.

The symptoms of the perforation of a tuberculous bladder ulcer are dependent upon the tissue into which the urine drains. The actual perforation of the bladder wall may not be accompanied by local pain (Pillet). If opening into the vagina, bowel or rectum, there may be no acute, unusual symptoms just prior to the perforation, or it may have been preceded by an aggravation of bladder symptoms for a few days. Subsequent to the perforation, the usual variation in the urinary act in a vesico-vaginal or vesico-rectal fistula is present.

Should the ulcer perforate into the tissues surrounding the bladder, the pain at the time of perforation may be severe (Caulk) or it may be but a sharp stinging sensation. It may be accompanied by shock and vomiting. Local tumefaction will soon appear and will be palpated in the perineum, about the prostate, in the hypochondrium, or in the groin, depending upon the point of perforation. The bladder irritability will be increased, the patient will strain to void and will void frequently and but small amounts. Catheterization will most often secure but a small amount of urine. The urine will be bloody. Neither catheterization nor voiding will

give relief. The local pain and swelling will increase and symptoms of sepsis will develop.

If the perforation is intraperitoneal, there is severe, sharp pain at the time of the perforation and evidences of a grave abdominal condition rapidly develop. At first generalized, the pain later tends to localize about the umbilicus. A rapid pulse, loose skin, nausea and vomiting, evidences of shock, are present. The bladder irritability is not increased (Alton, Laffitte) and may be lessened, (Stutzen). The patient passes but little urine, which is bloody, and catheterization most often finds the bladder empty. The abdomen soon becomes distended, rigid and hard. Free fluid can be demonstrated in the abdomen. The general course is that of a progressing peritonitis with impending death.

In an extraperitoneal perforation the bladder irritability is more marked, urination more frequent, and tenesmus and urgency more prominent symptoms immediately following the perforation than if the perforation is intraperitoneal, when in the latter, after opening into the abdominal cavity, the bladder tends to become more quiet and urination less frequent, and painful. The immediate pain is uniformly more severe in an intraperitoneal perforation. The intravesical injection and subsequent aspiration of measured quantities of fluid and the pneumocystogram will aid in establishing the presence of a perforation and in determining its position. Of the six cases of intraperitoneal perforation which the writer has collected, all six patients died, four having been operated on. Only very early recognition of this type of accident can offer hope to the patient.

When a vesico-vaginal or vesico-rectal fistula follows a perforation, surgical interest centers around its possible repair. Decision will be influenced by the local and general evidences of the patient's tuberculosis. Most frequently it will not be undertaken. Four attempts at repair were made in this series of vesico-vaginal fistulæ, all failures.

When the perforation opens into the prevesical tissues, drainage of the resulting abscess is necessary. To succeed in closing the urinary sinus which follows may prove extremely difficult. In Caulk's case of extraperitoneal perforation, it was ultimately necessary to isolate surgically by ureteral ligation the patient's only kidney, and to establish urinary drainage through nephrostomy.

If the perforation is into the peritoneal cavity, immediate surgical drainage of the abdomen and bladder is indicated. In none of the operated cases was there established adequate surgical drainage of both organs. Alton and Laffitte drained the abdomen surgically, but relied upon the anchored catheter for bladder drainage. Schürer established suprapubic bladder drainage, but closed the abdomen. Each operator has resected the necrotic area in the bladder. The bladder in each of the operated cases showed, at autopsy, profound septic changes with a necrotic bladder wall of varying degrees, while in two it was stated the autopsy disclosed the peritonitis subsiding and the abdominal condition satisfactory. It would seem then, to hope for a successful outcome in intraperitoneal perforation, special attention must be given the bladder in its surgical management.

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DISCUSSION

Dr. Hugh H. Young (Baltimore, Md.): Dr. Stevens' paper on the urachus interested me very much because a number of years ago, a doctor friend of mine brought his son, two years of age, with what he thought was a retrovesical sarcoma. The child was in considerable distress, pale and weak. There was a large round mass palpable just above the symphysis, which was fairly resistant, not absolutely hard, but looked very much like it might be a sarcoma. From the history, it seemed to have come first on top of the bladder and extended backward and upward. So I thought it might be an urachal cyst. With a very small cystoscope I found a dimpled condition of the urachus which was projected into the bladder. There was nothing coming out of the mass at all, but it was very red. I made a diagnosis of pyro-urachus. It was necessary to make only a small incision, and almost a quart of pus was evacuated. The point of insertion of the urachus is a point of weakness in the bladder wall. Pouches and diverticula are often seen there.

One of my cases, a young man, every now and then had a severe pain in the lower abdomen, which was thought to be appendicitis, for which he was about to be operated on. It was possible to get a very fine ureteral bougie up into it.

At operation I found the urachus patent for about 5 cm. The lower portion was strictured, and the upper portion slightly dilated and filled with purulent fluid. It was easily excised, and the bladder closed, with a complete cure. Attacks of pain had evidently risen from an accumulation of fluid above the orifice, which was occasionally closed spasmodically.

Dr. John R. Caulk (St. Louis, Mo.): I am very much interested in Dr. Mertz's presentation on spontaneous rupture in vesical tuberculosis.

He referred to my case, which was a very interesting one. It seems that many of these serious reactions occur in childhood, and while tuberculosis is virulent in children and is responsible for

about a 70 per cent mortality of those developing it within their first year of life and about 60 per cent of those in their second, due to massive lesions, some of those who live present very striking late lesions.

The little girl whom I reported developed spontaneous rupture of the bladder six or seven years after a nephrectomy for unilateral renal tuberculosis. She at this time complained of a sudden low abdominal pain, rapid development of a mass which ruptured over the anterior superior spine and from which a great deal of pus and urine was expelled. She presented herself with a sinus tract, which on examination was found to originate from a rupture of the posterior wall of the bladder at the site of an ulcer, and, as you see from the x-ray pictures, with the bladder and the cavities filled with sodium iodide, there is quite a large retrocystic cavity. The remaining kidney pelvis and ureter show pronounced dilation. In order to heal the bladder, I did a nephrostomy and fulgurated the bladder opening with high frequency. I saw her for several years afterward and the bladder had remained closed. I have lost sight of her for a number of years. It demonstrates how these indolent processes may remain quiescent and then suddenly create serious complications.

Dr. William F. Braasch (Rochester, Minn.): I have observed several cases of vesicovaginal fistula, such as Dr. Mertz described, in patients in whom we have removed tuberculous kidneys several years before, which apparently were of spontaneous development. It brings up the question whether it is possible to have tuberculosis of the bladder persisting for several years after removal of the tuberculous kidney, the remaining kidney being normal. I believe such a condition is possible.

In two cases of this type, I made repeated cystoscopic examinations and guinea pig inoculations from the kidney with negative renal findings. The finding of tuberculous ulcers and bacilli in the bladder would lead one to infer that tuberculosis of the bladder can persist for several years without tuberculosis in the remaining kidney.

I have observed one similar case very recently in which an extensive tuberculous granuloma was found in the bladder, which responded very nicely to intravesical application of a quartz lamp.

DR. A. J. CROWELL (Charlotte, N. C.): I would like to report a case of spontaneous vesico-vaginal fistula which resulted from gangrenous cystitis. This patient had a left nephrectomy in 1923 for multiple tuberculous abscesses.

In April, 1926, this patient was admitted to the clinic suffering with severe hematuria, frequency of urination, dysuria and partial retention. Within a few hours she passed a large membranous slough about the size of the palm of the hand. It was a complete cast of the bladder consisting of gangrenous mucosa, submucosa and some muscle bundles.

In August, 1930, she suddenly developed a seepage of urine and upon examination found a vesico-vaginal fistula which has persisted to the present time. Dr. L. C. Todd, our pathologist, examined the slough and diagnosed the condition tuberculous.

Because of the poor elimination of the remaining kidney and the undue nitrogenous retention, we were unable to do a transplantation of the ureter into the rectum. The patient was taken care of by means of retention catheter which Dr. Squires changed on an average of once weekly and thus kept the patient fairly comfortable.

DR. ALEXANDER R. STEVENS (New York City): I would like to call attention briefly to one point that is brought up by Dr. Young, in that his case of inflammatory reaction involved the lower end of the urachus. Almost all of the cases of inflammation of the urachus which I have found in the literature involve at least this end adjacent to the bladder. In a good many instances it comes fairly high and occasionally runs all the way up to the umbilicus.

About a year ago, Dr. Squier reported three cases, and all of these had very marked inflammation adjacent to the bladder. Also, it is usual that cases of this sort have a patent termination, either at the bladder end or at the umbilicus. Our case is unusual in that it did not have any open connection with either the umbilicus or the bladder and that the inflammatory involvement was of the upper end only.

DR. HENRY O. MERTZ (Indianapolis, Ind.): We, in going through the literature, were interested in seeing whether we could

draw any conclusions concerning the actual forces involved in the development of a vesical-vaginal perforation in these cases. I rather think that, from what I have gathered, it is not the actual extension of the tuberculosis itself through the bladder—at least I base that on the negative tissue examination in many of the cases in which the ulcer has been examined thoroughly—but that there is a definite bacterial thrombotic condition in the vessels surrounding the perforation. So probably the thing that actually happens is that a bacterial thrombus forms in a tuberculous ulceration and that the perforation is due to mixed infection, rather than to the tubercle germ itself.

PRIMARY CARCINOMA OF THE URETER

HARRY A. FOWLER, M.D.
Washington, D. C.

Three years ago I reported before this Association a case of papilloma of the ureter associated with recurring papillomata of the bladder, the only recognized case of this kind which has come under my personal observation. I had occasion at that time to review the literature of tumors of the ureter and was impressed with the apparent rarity of this condition.

The earlier cases reported were obtained from autopsy records. Gradually, as our methods of exact study and diagnosis were improved and extended, the condition was recognized clinically so that in some of the later cases a complete clinical study is presented. The cases which come to operation have gradually increased in number during the past few years until now we have a considerable amount of material available in the form of complete clinical records from which certain conclusions may be drawn as to the surgical management of this condition and the ultimate results that one may expect to obtain by such treatment.

That primary tumors of the ureter are relatively uncommon is evidenced by the fact that at the time of the report referred to I was able to collect only fifty-three cases of malignant growths and thirty-four cases of papilloma. Since that time a considerable number of additional cases have been reported.

In addition to its rarity a tumor of the ureter, whether primary or secondary, so-called benign or malignant, is a serious lesion. It is serious by reason of the obstruction of the ureter which it produces, often causing complete destruction of the corresponding kidney. Indeed, in many of these cases the kidney is completely destroyed when the patient comes under observation and the enlarged hydronephrotic kidney dominates the clinical picture. More particularly, however, the condition is a serious one because of the unfavorable prognosis which it carries. In the so-called benign papilloma group, experience has shown that a combined nephroureterectomy with removal of the vesical end of the ureter offers

the safest guarantee against recurrence. In the malignant tumor group such radical surgery, even when indicated, is unable to cope with widespread metastasis. The prognosis in this group is essentially bad.

The following observation illustrates this point and adds another case report to the increasing number recorded in the literature.

F. T. C., aged sixty-one years, was admitted to the Naval Hospital in October, 1931, with a history of intermittent hematuria covering a period of eight months.

He was first seen in the out-patient department of the hospital several weeks before admission, stating that four months previously he had "found a little blood in his urine." At the time of his visit the urine was distinctly tinged with blood. This promptly cleared and remained so for two months when the hematuria recurred, lasting three or four days. During this attack he passed a long worm-like clot. This history was repeated several times, the attacks becoming more frequent. Finally, after passing several small clots, he was prevailed upon to enter the hospital for routine study.

Family History.—The father died of cancer of the rectum and bladder at sixty-eight years. Otherwise the family history was good.

There is nothing of importance in his past history bearing upon his present trouble.

The night before admission he passed an elongated clot about the thickness of a lead pencil and two inches long. This was dark in color, rather soft, and had the appearance of a partially organized clot. The urine contained gross blood. The clot was sent to the laboratory for study. The report stated it contained poorly staining cellular elements some of which showed a papillary arrangement, and the probable diagnosis of malignancy was made.

General physical examination was essentially negative. The blood picture was normal. Cystoscopy showed a prominent right ureteral ridge, the ureteral orifice suggested the golf-hole type with some strands of blood clot protruding from the orifice, and with each peristaltic wave a faint stream of blood was seen issuing from the orifice. The mucosa about the orifice was congested. An impassable obstruction was encountered 1 cm. above the orifice.

The first x-ray examination, including intravenous urography, was unsatisfactory due to an enormous amount of gas in the bowels. A second x-ray examination was negative for stone shadows. Intravenous skiodan showed a normal left kidney and ureter. There was no concentration of the contrast medium in the right pelvis or ureter and the outline of right kidney was not well visualized.

Obstruction in the right ureter was thought to be due to a blood clot: the probable diagnosis of neoplasm of right kidney or right ureter, or both, was made.

We saw the patient in consultation at this time, concurred in the diagnosis and recommended exploration of kidney, and probably a nephrectomy.

Right nephrectomy and partial ureterectomy were done January 8, 1932, under spinal anesthesia. The kidney on exposure was lobulated, the pelvis markedly distended and the ureter dilated. On delivering the kidney, the thin distended pelvis was slightly torn and a brownish colored fluid escaped. A vessel to the upper pole was identified and ligated. The kidney with a segment of the ureter was easily removed.

The kidney on gross examination was found to be very small, the cortex thinned by compression, the pelvis contained a moderate sized fresh blood clot. There was no evidence of intrarenal tumor. The diagnosis of hydronephrosis, hydro-ureter was confirmed by histologic examination.

Convalescence was smooth and rapid, the patient leaving the hospital on the thirteenth day (January 21, 1932). The following day the urine was discolored with fresh blood for the first time after operation. Twenty-nine days after operation the patient passed a large single mass of what appeared to be fibrin. This seemed entirely too large to have escaped from the ureter. The urine was again blood tinged. Dr. Wildman, pathologist, described this voided material as follows: "It consists of a papillary or polypoid type of tissue, brownish-gray in color, in which fine leaf-like prolongations extend out from the basal stock. The thickest one is 0.5 cm. in diameter and 2.0 cm. in length, the others are considerably thinner. The cells are completely necrotic and fail to take the differential stains. The general structure of the tissue suggests a polypoid formation. No conclusion as to malignancy can be given due to the necrotic condition of the cells. Pathologic diagnosis: necrotic tissue."

Intermittent hematuria continued, slight at first, but the attacks becoming more severe with the passage of small clots. We were delaying a second operation for removal of the lower ureter to allow improvement in the patient's general physical condition. However, the increasing frequency and severity of attacks of hematuria demanded action, and the patient re-entered the hospital for routine study. Inspection of the bladder for the first time by us showed a pronounced hypertrophy of the right side of the trigone with the right ureteral opening placed on the summit of a rather large ureteral papilla. The left side of the trigone was normal. The bladder was otherwise normal. Clear urine was escaping from the left ureteral orifice. A catheter was introduced into the right ureteral orifice, meeting an impassable obstruction at 4 centimeters. Injection of the ureter with contrast solution failed to give us additional information as this escaped into the bladder. This examination was repeated with a Garceau catheter with the same results.

At a subsequent cystoscopy a blood clot was seen filling the right ureteral orifice. In the meantime another mass of necrotic tissue had

been passed with the urine. Increasing severity of the bleeding secured the patient's consent to the second operation for removal of the lower segment of the right ureter. Operation was performed May 10, 1932, under spinal anesthesia. On exposure the ureter was found to be thickened to the size of one's thumb at the point where it passed over the iliac vessels, irregular, nodular, very hard like cartilage and densely adherent to the peritoneum and surrounding structures. Great care was necessary in separating the peritoneum at this point and also freeing the mass from the iliac artery to which it was intimately attached. The remainder of the ureter was easily separated, ligated and cut well below the area of induration and near the bladder wall. Convalescence was smooth, afebrile, and the patient left the hospital on the twelfth day.

The specimen was examined by the pathologist at the Naval Hospital, who reported as follows:

"Gross examination: Specimen consists of a resected portion of ureter measuring 7 by 2 centimeters. The wall is greatly thickened by fibrosis. Mucosa is ulcerated and replaced by a brownish-white, rather soft tumor mass which fills the lumen.

"Microscopic: Sections of ureter show destruction of the mucosa by anaplastic epithelial growth and suppurative inflammatory reaction, with large amounts of necrotic tissue in the lumen. Wall is thickened by fibrosis and infiltrated by large masses of non-cornifying epithelial cells which are large and hyperchromatic with numerous mitoses.

"Pathologic diagnosis: Carcinoma, squamous cell—ureter."

Postoperative Course.—The patient was comfortable for one month except for low backache coming on after sitting up for some time. At this time a slight discoloration of the urine with blood was noted for the first time after second operation. This continued at intervals up to his death six months after operation, but was never severe in amount and practically symptomless. Pain referred to the lower back on each side and the region of the right anterior superior spine of ilium was his chief complaint. He tired easily from exercise. The persistent backache was treated by diathermy at the Naval Hospital. It was thought the x-ray treatment was relieving his pain, but this became again very severe. There was no evidence of metastasis either on clinical or x-ray examination. This was just three months after his second operation. The pain continued so severe as to require opiates. It became more diffuse, at times referred to the left shoulder. All efforts to find a local cause were unavailing. Another x-ray examination again failed to show any bone metastasis.

Four months after operation he began to show definite signs of emaciation, although he was taking sufficient nourishment. Pain was the dominant symptom, difficult to control even with a liberal use of opiates. Six weeks before death, marked tenderness and rigidity of the right abdomen developed. The pain gradually diminished somewhat in intensity. Two weeks later definite enlargement of the liver could

be made out. This rapidly increased and filled the whole upper right abdomen, pushing the abdominal wall forward. The patient was able to go to the bath room up to ten days before death. Weakness gradually increased and he finally died on November 10, 1932, six months after removal of the ureter. No autopsy was made.

COMMENT

In this clinical report details of the general physical examination, numerous laboratory tests and x-ray examinations have been omitted for the sake of brevity. The patient was an officer of high rank in the service, all examinations were made with meticulous care and thoroughness. The essential findings reported indicate no demonstrable lesion outside the urinary tract. This point is mentioned as confirming our conviction that the lesion in the right ureter was primary and to forestall any criticism that the records in the case are incomplete.

Attention is called to the fact that pre-operative study gave positive evidence of (1) hematuria of right upper tract origin, (2) impassable obstruction in the right lower ureter, (3) a functionless right kidney, and (4) that the underlying causative lesion was presumably malignant disease of either the kidney, the ureter, or both. This latter fact was evident from the histologic examination of material voided by the patient previous to operation. This showed faintly but definitely a cell structure indicating a malignant neoplasm. It was impossible to determine by any of our usual methods of examination the character and extent of any structural changes within the right kidney. All we could determine by our study was that it was functionless. For this reason it seemed wise to explore the kidney first with the probability that a nephrectomy would be in order. It was only by carrying out this plan of procedure that we were able to determine definitely that the primary lesion was in the lower ureter and not in the kidney. It was our belief based upon all the available data at hand, that a nephro-ureterectomy as a primary operative procedure was not indicated. And I am convinced by the subsequent course of events that this judgment was correct. A combined operation would have been difficult and, in my hands at least, prolonged, thus greatly increasing the surgical hazards. Furthermore, it may be observed that the extension of the disease beyond the primary site in the ureter had unquestionably occurred before the first operation.

This brings up the question of metastasis in these malignant growths of the ureter. A review of the published cases indicates that metastasis occurs relatively early. This is supported by our observation. If such is the case, and there appears no good reason for doubting it, early diagnosis and complete extirpation offer the only hope of preventing widespread metastasis. Unfortunately, our observation furnishes no data bearing upon the question of how or by what route metastasis occurs. We can only say that the liver was the site of an enormous metastatic growth. The duration of the disease from the outset of the first symptom, hematuria, to death from metastasis was twenty-one months.

The only presenting symptom was a symptomless hematuria, never abundant in the early stages. It was intermittent in character and continued four months before the patient came under observation and another four months before he consented to a routine urologic study. In the meantime the kidney had become silently destroyed by a gradually increasing ureteral obstruction. In the light of such an experience the possibility of early diagnosis and early application of appropriate surgical treatment in many cases in this group appears to be not very promising.

PRIMARY TUMORS OF THE URETER

WITH PRESENTATION OF A NEW METHOD OF COMPLETE NEPHRO-URETERECTOMY

J. A. C. COLSTON, M.D.

From the Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

A recent case, finally proven to be a primary tumor of the ureter, a diagnosis which was confirmed at operation, presented in addition to the interest which was occasioned by this rare condition, the hitherto unreported complication of implantation of the primary tumor in a diverticulum of the bladder. In view of this unusual complication and the fact that the patient has been observed over a period of twenty-six months and has been well a year following the last operation, it seemed advisable to report this case in full, to search the records of the hospital for further instances of primary tumors of the ureter and to review the literature.

It is known, of course, that primary tumors of the ureter are quite rare, that the diagnosis presents certain difficulties, but that if an early diagnosis is made the ultimate prognosis from operative therapy in most cases should be excellent, provided the proper operative steps are carefully carried out.

The records of the Brady Urological Institute, comprising over 22,000 urological cases, contain three instances of primary tumor of the ureter. In addition there are several instances of implantation of tumor into the ureter, secondary to a primary tumor of the kidney. These cases have not been included in this series, nor has another interesting instance in which a small tumor was discovered at the ureteral orifice, probably secondary to a bladder tumor which had been destroyed two years previously.

Case 1.—D. E. B., male, aged forty-six years, a patient of Dr. Hugh H. Young, entered the hospital January 27, 1931, complaining of hematuria, which was first noted three years before. There were no urinary symptoms, but a dull ache had been present in the right lumbar region for about a week. All symptoms then cleared up and the patient was perfectly well. Blood was again noted in six months' time, also ac-

companied by pain, but the symptoms again cleared up. A third attack of hematuria and dull pain occurred a year later. Cystoscopic examination was made at this time and blood was found coming from the right

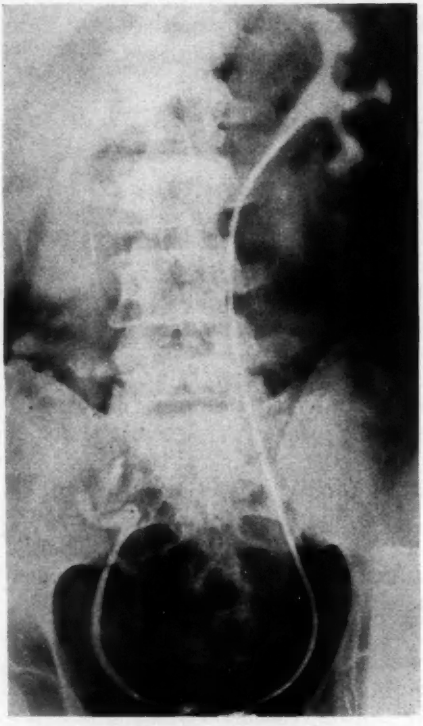

Fig. 1. Double pyelo-ureterogram, pre-operative. The catheter in the right ureter meets an impassable obstruction 3 inches from the bladder. Attempted ureterogram shows only a small amount of opaque medium in the ureter, which is markedly distorted, and the irregular outline of the shadow should suggest a filling defect.

ureteral orifice. An attempt was made to catheterize this ureter, but obstruction was encountered in the lower third, and the catheter could not be passed to the kidney. A month later cystoscopy was carried out and a diverticulum of the bladder was noted. At about this time,

a year before admission, the patient noticed that the urine became cloudy with some blood on the slightest exertion. There was rather persistent pain in the right kidney region referred to the groin and testicle. Slight nocturnal frequency also became evident. He noted that he had become progressively weaker with lack of energy and attacks of drowsiness.

On examination the patient was well nourished, and well developed. There was no evident recent loss of weight. The chest, lungs and heart

Fig. 2. Right kidney following nephrectomy. A marked grade of obstructive hydronephrosis is present.

were essentially normal. The abdomen was normal and neither kidney could be felt. On deep pressure over the left kidney, tenderness was noted. There was no tenderness over the right kidney or in the costovertebral angle. The external genitalia were normal. The urine was hazy in two glasses, showed a slight trace of albumin, a moderate number of white cells, but no organisms. On rectal examination the prostate was of normal size and no indurated areas were noted. The phthalein test showed an excretion of 35 per cent for the first half hour, 28 per cent for the second half hour, and 14 per cent for the second hour, a total of 78 per cent.

Cystoscopic examination showed no residual urine. The bladder capacity was 500 c.c. There was no intravesical enlargement of the lateral lobes, but a small median bar was present. The trigone was moderately hypertrophied and the bladder showed slight trabeculation. Just external to the left ureter was seen the orifice of a large diverticulum. A ureter catheter entered the right ureter for a distance of 3

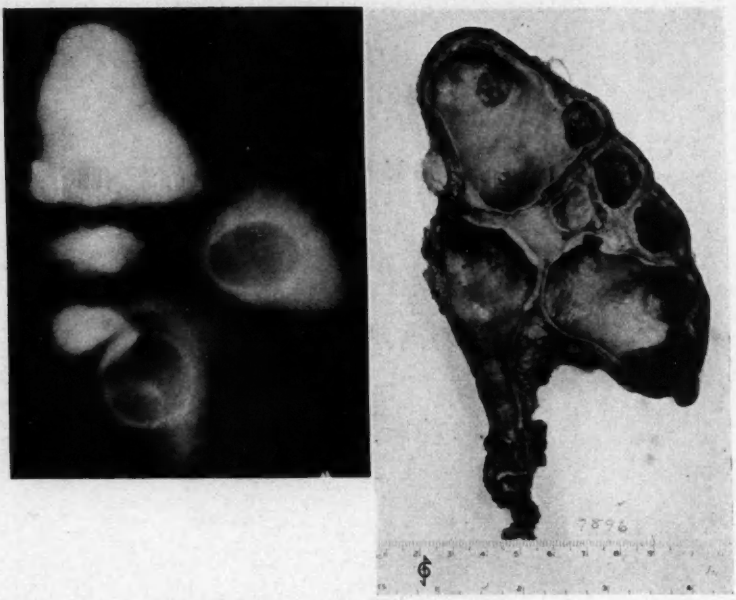

Fig. 3. Post-operative pyelogram, right kidney, showing marked grade of obstructive hydronephrosis.

Fig. 4. Longitudinal section of right kidney, showing marked grade of hydronephrosis with almost complete destruction of secreting tissue, dilated pelvis and tortuous ureter.

inches, where it met an impassable obstruction. A catheter ascended to the left kidney without meeting any obstruction. No function was obtained from the right side, although a few drops of blood came out of the catheter. From the left catheter clear urine was obtained containing no pus cells or organisms and the function was 50 per cent in thirty minutes.

A plain x-ray showed the kidneys apparently of normal size and in normal position. Neither kidney was enlarged. A bilateral pyelogram

(Fig. 1) was attempted, which showed the pelvis of the left kidney to be of normal outline with no evidence of distortion or dilatation. The pyelographic medium was obstructed on the right side above the brim of the pelvis, the ureter being slightly dilated with a kink, and the

Fig. 5. Pre-operative right ureterogram. The opaque medium has been injected under increased pressure. The lower end of the ureter is dilated and at the point of obstruction there is a typical filling defect. A small amount of opaque medium has been injected through the mass of tumor tissue, giving a typical irregular shadow, with evidence of filling defect. At the upper end of the ureter near the site of its previous ligation following nephrectomy there is an area of irregular distention.

upper edge of the shadow was somewhat irregular. The solution did not reach the kidney pelvis. Films taken after intravenous skiodan were not satisfactory. A diagnosis of functionless right kidney, due to obstruction in the right ureter, was made. The presence of the diver-

ticulum was hard to understand in view of the fact that there was no marked demonstrable obstruction at the prostatic orifice.

The patient returned to the hospital on March 18, 1931. Another attempt was made to catheterize the right ureter, but again obstruction

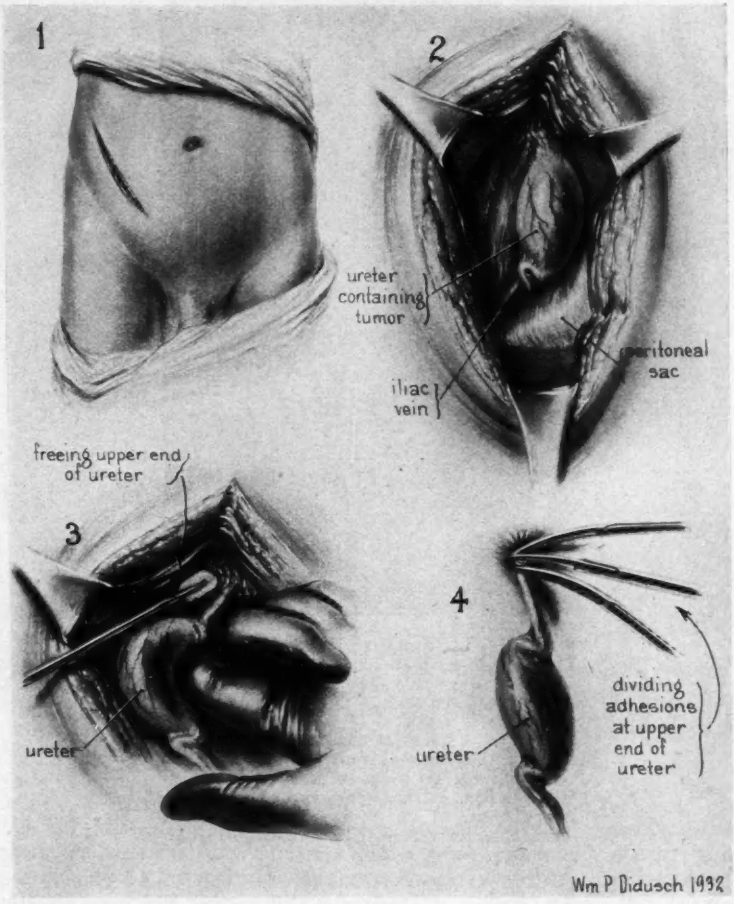

Fig. 6. The technic of complete uretero-nephrectomy: *(1)* Muscle splitting incision paralleling Poupart's ligament. *(2)* Exposure of lower ureter. *(3)* Dissection of lower ureter from surrounding tissue. *(4)* Division of adhesions and scar tissue about stump of upper ureter.

was met 3 inches from the orifice. On March 20, 1931, under ethylene anesthesia, right nephrectomy was done by Dr. Colston. The ureter was found dilated to about three times normal size. It was ligated 2

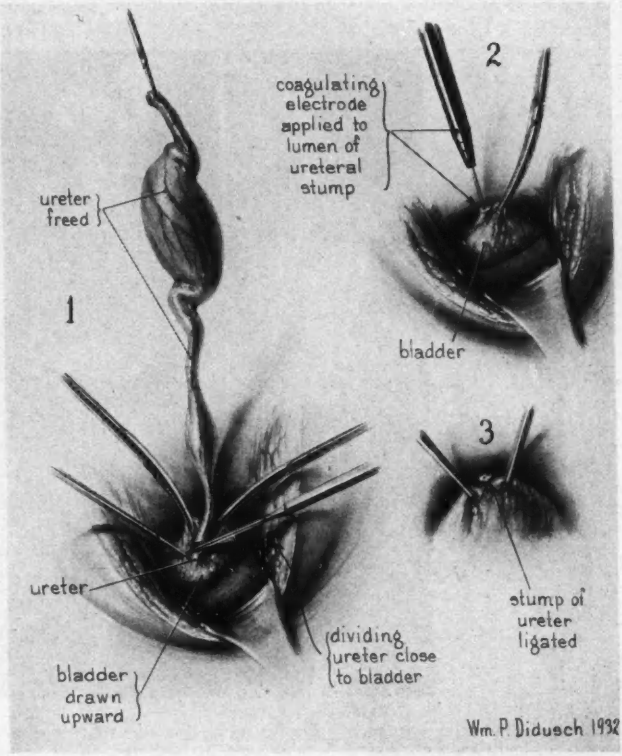

Fig. 7. The technic of complete uretero-nephrectomy (continued). *(1)* The upper ureter has been dissected free from surrounding tissue. The ureter is divided by means of the cutting cautery just above its entry into the bladder wall. *(2)* The edges of the stump of the ureter are caught with clamps and the coagulating electrode is introduced into its lumen, passed through its entire extent to the ureteral orifice, thus destroying its entire mucosa. *(3)* Ligation of the stump of the ureter after its mucosa has been destroyed.

inches below the pelvis, no attempt being made to explore its lower portion. The kidney was removed in the usual manner without difficulty.

The pathologic specimen (Fig. 2) showed a markedly hydronephrotic kidney with adherent capsule and perirenal fat. The post-operative pyelogram (Fig. 3) showed hydronephrosis with marked destruction of secreting tissue. On section (Fig. 4) the kidney was divided into lobules and there was practically no renal substance to be

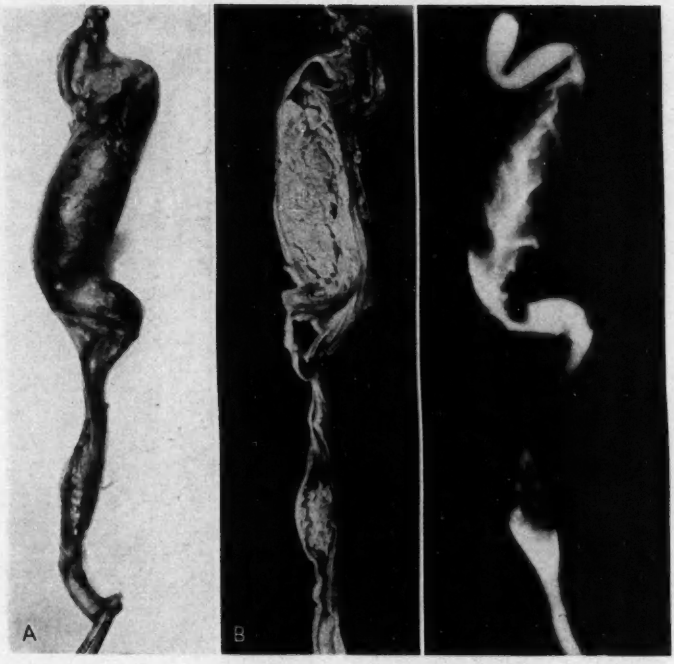

Fig. 8. *(a)* Operative specimen. The tortuous dilated ureter is clearly seen with a clamp on its lower end. *(b)* Longitudinal section of operative specimen showing large tumor mass almost occluding the ureter and two small masses of tumor implantation in the lower course of the ureter.

Fig. 9. Post-operative ureterogram. The opaque medium has been injected under pressure, and can be seen infiltrating between the tumor mass with typical appearance of filling defect.

made out. No stone was present. The lining of the hydronephrotic cavity was pearly white and there was nowhere any evidence of tumor. Microscopic section showed the capsule considerably thickened with a small amount of greatly compressed kidney tissue, infiltrated with round cells and fibrous tissue so that only a few glomerular tufts were

seen, with only a few distorted kidney tubules. No evidence of tumor was seen.

The postoperative convalescence was complicated by some superficial infection of the wound. The patient was discharged on April 15, 1931, in good condition.

The patient re-entered the hospital on December 15, 1931. He had regained his strength rapidly following the operation and the wound was completely healed. However, about six months later, he had noticed gross hematuria unassociated with any other symptoms. This

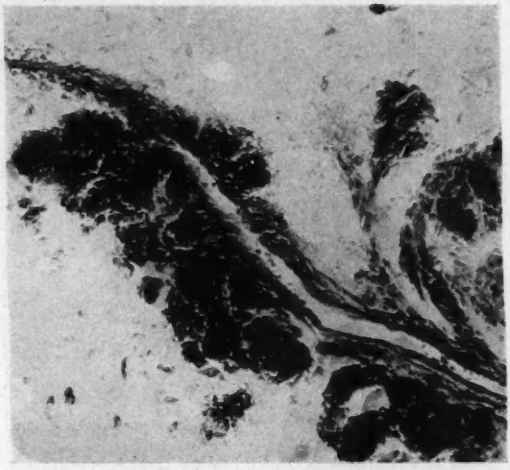

Fig. 10. Microscopic section of ureteral tumor, showing typical papillary appearance.

bleeding continued, intermittent in character and variable in duration, but gradually became more pronounced. During the past week, he had noticed some sharp intermittent pain in the right lower quadrant. On December 11, 1931, cystoscopic examination revealed no obstruction at the prostatic orifice. The orifice of the diverticulum was present as before. From the right ureteral orifice a definite blood clot could be seen extruding across the base of the bladder. A Garceau catheter was introduced and a ureterogram was done, which showed the ureter dilated, tortuous and thickened with a characteristic irregularity of the upper portion of the shadow (Fig. 5). A diagnosis of tumor of the ureter was made. On physical examination on admission the findings were similar to those found on his previous admission except that a small indefinite mass was felt in the right lower quadrant.

On December 16, 1931, under spinal anesthesia, a right ureterectomy was done by Dr. Colston through an extraperitoneal incision (Fig. 6, *1*). The enlarged thickened ureter (Fig. 6, *2*) was found to contain a mass which extended down toward the bladder. However, 2 inches from the bladder the ureter became of normal size. The ureter containing the mass was dissected upward (Fig. 6, *3*). Here again the ureter tapered off and became of normal size, for a distance of about 2 inches, where the site of its previous division was encountered.

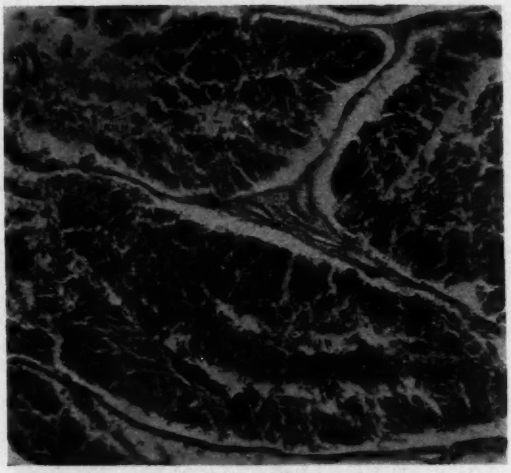

Fig. 11. Microscopic section of ureteral tumor, showing typical papillary morphology with marked proliferation of the epithelial layers. Under the high power these epithelial cells are seen to be cuboidal and transitional in type and many mitotic figures are seen. A diagnosis of papillary epithelioma was made.

The whole ureter was then brought up into the wound and dissected free (Fig. 6, *4*). It was clamped just above its entrance into the bladder and divided (Fig. *7*, *1*). The edges of the distal stump were then grasped with clamps. The fulgurating electrode was passed down through the lumen of the ureter (Fig. *7*, *2*) which was thoroughly fulgurated for the purpose of destroying any implantation which might have been present in the lower segment of the ureter. The stump was then ligated with catgut (Fig. *7*, *3*) and the wound closed in the usual manner with drainage.

The specimen removed (Fig. 8, *1*) consisted of a dilated, thickened ureter measuring 15 cm. in length. The postoperative ureterogram

(Fig. 9) shows the tumor areas beautifully outlined in the ureter. There were several kinks in the ureter with some peri-ureteral fibrous tissue. On opening the ureter two sharp S-shaped kinks and two fusiform enlargements were seen, the latter entirely filled with friable papillary tumor which was a dirty gray in color (Fig. 8, *2*). Microscopic examination (Figs. 10 and 11) showed smooth muscle in circular formation, surrounded by loose areas of areolar tissue. The mu-

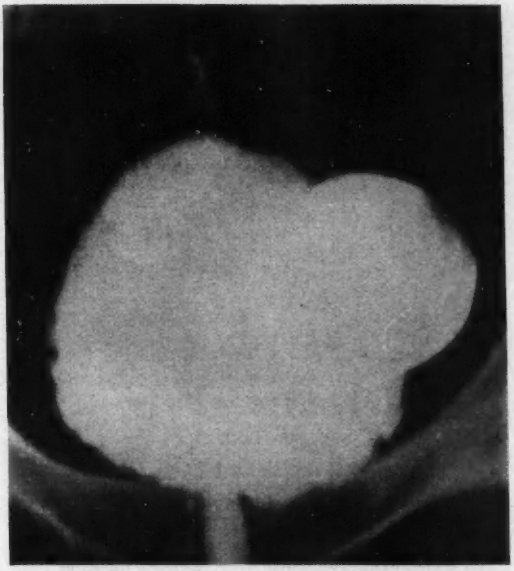

Fig. 12. Pre-operative cystogram. Bladder is slightly dilated and shows evidence of trabeculation. Springing from the left lateral aspect is a large diverticulum, the circumference of which is clearly outlined except for a definite filling defect on its left lateral margin.

cosa had been entirely replaced by a papillary tumor, consisting of long branching strands of fibrous tissue carrying blood vessels and growing out from the side of the ureter. These papillary processes were covered with thick layers of transitional epithelial cells, some being spindle-shaped and some polyhedral. The nuclei were small and darkly staining. No mitotic figures were seen. The tumor tissue apparently did not invade the submucous tissue, except in one section, where, however, the tumor tissue did not penetrate through the muscular layer.

The patient's convalescense was complicated by a secondary hemorrhage, followed by secondary infection of the wound. He left the hospital on January 30, 1932. He regained his strength rapidly, but several months later again noted the appearance of blood in the urine. This persisted at intervals, but gradually increased and was accompanied by slight burning and frequency.

On March 14, 1932, cystoscopy was undertaken to determine the source of the bleeding. Slight obstruction was encountered at the

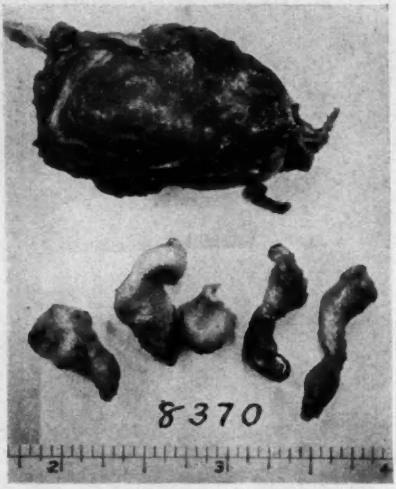

Fig. 13. Operative specimen. The excised diverticulum has been packed with a sponge. Five pieces have been removed from the prostatic orifice by punch operation under direct vision.

neck of the bladder. A catheter was introduced into the stump of the ureter, but ascended only 2 cm., and no bleeding occurred after manipulation. The left ureter was easily catheterized. The urine from the left kidney was clear with no blood, and microscopic examination showed no pus cells and no infection. A cystogram was done (Fig. 12) which showed a diverticulum measuring about 4 cm. in diameter on the left side of the bladder. The outline of the diverticulum was perfectly smooth except for a small filling defect which was present on its upper left aspect. A diagnosis of implantation of the original tumor from the right ureter into the diverticulum was made.

On June 22, under spinal anesthesia, the bladder was opened supra-

pubically by Dr. Colston, after preliminary mobilization with special attention to the left side. The orifice of the diverticulum was explored and fresh blood was observed oozing from it. A catheter was introduced into the left ureter so as to avoid injury to this structure. The right ureteral orifice could not be definitely seen and there was only slight superficial scarring present. No evidence of tumor could be made out anywhere throughout the bladder. The diverticulum was then packed with a sponge and the orifice grasped with clips. It was

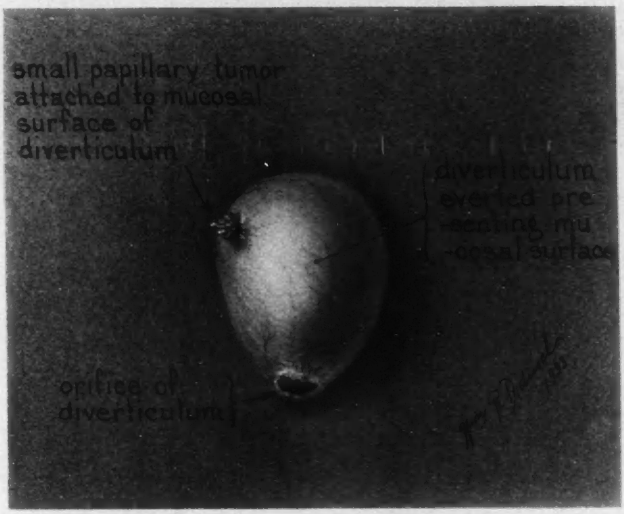
small papillary tumor attached to mucosal surface of diverticulum
diverticulum everted exposing mucosal surface
orifice of diverticulum

Fig. 14. The diverticulum has been everted about a sponge to expose its mucosal surface fully. On the upper left portion of the mucosal surface can be seen a small papillary tumor.

excised intravesically without difficulty. The prostatic orifice was examined and a definite contracture found present. Under direct vision a punch instrument was introduced and five cuts were made until the orifice was found satisfactorily relaxed. The bleeding was controlled by the fulgurating electrode. Closure was carried out in the usual way with extravesical drainage and a tube in the bladder.

Pathologic examination (Fig. 13) revealed a rounded thin-walled sac, the mucous membrane appearing shiny without evidence of ulceration. Near the bottom of the sac and projecting from the mucosa was a small papillary tumor with a narrow pedicle (Fig. 14). The tumor measured only about 5 x 4 mm. In preparing the microscopic section the small tumor was lost or destroyed. The wall of the diver-

ticulum showed a fibromuscular stroma with a lining of columnar epithelium. The epithelium showed marked proliferation and chronic inflammatory change.

The patient's postoperative convalescence was complicated by a left sided pyelitis which, however, subsided under expectant treatment. He left the hospital on June 27, in excellent condition. The phthalein test on discharge showed an appearance time of four minutes, and excretion of 85 per cent in two hours.

He was seen again on October 11, 1932, and was in excellent condi-

Fig. 15. Microscopic section (Case 3), showing a typical infiltrating squamous epithelioma. No epithelial pearls can be seen in this section.

tion. His general health was good, he had regained his weight completely and was entirely free from symptoms except for slight irritation and slight urgency. He had had no recurrence of the hematuria. On examination the scars of the three operations were well healed. The urine was clear, contained no albumin, no sugar, and microscopically no red cells, an occasional white cell and occasional epithelial cell.

Comment.—Although a diagnosis of tumor of the ureter was finally made and the ureter with the tumor was successfully removed at operation, from a study of the case in retrospect, it would only be fair to state that this condition should have been recog-

nized at the original examination. It will be recalled that the catheter met obstruction in the lower third of the ureter and that the procedure was followed by a considerable flow of blood from the catheter. In addition, the ureterogram (Fig. 1) shows an irregular dilatation in the lower third of the ureter with a marked irregularity of the upper limit of the pyelographic medium which should have suggested a neoplasm. A nephrectomy was done under the impression that the kidney had been destroyed as a result of some unknown obstruction in the lower portion of the ureter. The lower part of the ureter was not explored at operation. It is fortunate, however, that this failure to make the correct diagnosis at the original examination did not affect the ultimate result, as an accurate appreciation of the situation was realized and the proper operative procedure instituted before the tumor had extended through the wall of the ureter.

Case 2.—Mrs. B. H. J., aged fifty, a patient of Dr. W. A. Frontz, came September 24, 1917, complaining of bladder trouble. The past history was unimportant. She had first noticed frequency eighteen years previously and at the same time had noted the presence of blood in the urine. The frequency and burning had persisted at intervals and the hematuria had become more and more pronounced. The patient had developed a morbid fear of having contracted syphilis and this condition had developed into a very pronounced syphilophobia. She had been catheterizing herself for the past four years under the impression that a syphilitic paralysis of the bladder was present.

The general physical examination revealed no abnormality. The Wassermann reaction was negative. The urine was cloudy, contained pus cells, red cells and numerous organisms. Cystoscopic examination revealed no obstruction at the internal orifice. There was no evidence of either atrophy or hypertrophy of the bladder musculature. The patient refused to enter the hospital and no further studies were made at that time.

She was seen again on March 27, 1919, complaining of urinary retention and she thought it was necessary to catheterize herself three times in twenty-four hours, when she noted a little obstruction at the neck of the bladder. She was able to void some urine with varying degrees of ease.

On cystoscopic examination 400 c.c. of cloudy urine was found in the bladder. No obstruction was seen at the internal orifice, but slight definite trabeculation was noted. The trigone was smooth but not atrophic. The bladder mucosa showed everywhere a slight degree of chronic inflammation. During the next few months she was treated

by dilatation of the internal orifice and application of silver to the urethra with marked improvement in the retention.

On October 9, 1919, cystoscopic examination first revealed a bulging of the right ureteral ridge and in the ureteral orifice was seen some necrotic tissue and mucus. A catheter could be introduced for only a distance of 1 cm., causing considerable bleeding. A plain x-ray showed the kidney shadows of normal size and in normal position. There was no evidence of stone in the kidneys or along the course of the ureters. The patient still refused to enter the hospital, and during the next month experienced considerable pain in the right lumbar region, together with intermittent hematuria.

On November 3, 1919, cystoscopic examination revealed a sausage shaped mass bulging from the right ureter. The surface of this mass was irregular and edematous and the terminal portion was covered by grayish white slough. She still refused to enter the hospital and during the next few months experienced continuous dull pain in the right kidney region.

On account of these symptoms she entered the hospital on February 28, 1920. Physical examination revealed no abnormalities, the patient being well developed and well nourished. On pelvic examination a moderate grade of relaxation was found. The urethral orifice was normal and there was no evidence of infection. The cervix was normal. The base of the bladder on the left side, the lower end of the left ureter and left fornix were normal. Protruding into the right fornix and extending from the region of the lower end of the right ureter up to the pelvic wall was a small rounded tumor. It was attached to the pelvic wall by a broad base, was absolutely fixed and of stony hardness. On rectal examination it was not connected with the bowel, nor definitely with the ureter. On account of the fixation of the mass it was felt that the neoplasm had infiltrated the ureteral wall and surrounding tissue, to such a degree as to make complete removal impossible.

The patient left the hospital and refused to return. She was seen at intervals and her course was progressively down hill. Before death, about five months after leaving the hospital, a large mass was palpable in the right lower quadrant. Death was due to uremia and cachexia of malignant disease. No autopsy was obtained.

Comment.—The diagnosis in this case presented especial difficulty. The true condition was not suspected at an early date on account of the unusual bladder condition. The presence of blood was thought to be a result of repeated catheterization and the the chronic inflammation present. Two years after the patient was first seen, a bulge of the ureteral ridge was first noted on cystoscopic examination. A catheter could be introduced for only a

short distance and this procedure was followed by considerable bleeding. X-rays were of no value in establishing the correct diagnosis on account of the inability to introduce a catheter. The lack of coöperation on the part of the patient also played an important part in preventing an accurate diagnosis until the condition was too far advanced for any therapeutic methods.

Case 3.—Mrs. C. K., aged sixty-two, entered November 30, 1926, complaining of blood in the urine, duration two months, and dull pain in the left flank. The past history was unimportant. The patient had noted blood in the urine during the past two months. There had been slight nocturia and some burning on urination. For the past few weeks she had noted dull pain in the left lumbar region. There had been no loss of weight.

General physical examination revealed no abnormalities except hypertension. There was also slight tenderness on deep pressure in the region of the left kidney. The urine showed albumin, many red cells, a few white cells, but no organisms. A pelvic examination revealed no abnormalities except a moderate degree of cystocele. There was some tenderness over both ureters, but no mass could be felt. On cystoscopic examination by Dr. Frontz, the external orifice was normal. The bladder mucosa was everywhere smooth and normal and no tumor was seen. A catheter entered the right ureter and met definite obstruction in the region of the broad ligament. A catheter was introduced into the left ureter and passed to a point just below the kidney where obstruction was encountered and free bleeding occurred. A double pyelo-ureterogram showed the right kidney pelvis considerably enlarged, with the ureter dilated down to its entrance into the bladder. The outline of the left kidney was not clearly seen. The kidney was apparently considerably enlarged. The left ureter was uniformly dilated throughout its extent but there was no pyelographic medium in the pelvis. A tentative diagnosis of stricture of both ureters was made. Cystoscopy was done again on December 9 and December 30, 1926, and on each occasion x-ray films showed a deviation of the catheter toward the spine, the tip of the catheter stopping at the pelvic brim.

On January 21, 1927, on account of the persistent hematuria the left kidney was explored by Dr. Hunner. The kidney was found to be of normal size, but the pelvis was markedly dilated. The ureter was also dilated to a diameter of 5 cm. The ureter was opened with evacuation of cloudy urine, and after some difficulty a catheter was passed down to the bladder, meeting definite obstruction in the lower ureter. The wound was closed with drainage. A diagnosis of hydronephrosis, hydro-ureter and stricture of the left ureter, was made.

The postoperative course was uneventful. On February 12, 1927,

the left ureter was again dilated, obstruction being met in the lower third, and some bloody urine was obtained.

The patient re-entered the hospital April 28, 1927. Physical examination was again essentially negative. The operative incision was well healed. On cystoscopic examination a catheter introduced into the left ureter encountered a marked obstruction in the lower ureter. Intravenous phthalein showed excretion of 30 per cent in a half hour from the right side. From the left side only a trace was secreted. A left pyelo-ureterogram showed marked dilatation of the left ureter with a marked grade of hydronephrosis. A cystogram showed flattening of the outline of the bladder on the lower portion of the left side.

On May 27, 1927, left nephrectomy was carried out, the dilated ureter being ligated in the usual way without exploration of the lower portion.

The postoperative course was uneventful and the patient was discharged on June 5, 1927.

The patient re-entered the hospital on July 4, 1927, on account of pain in the lumbar region with some elevation of temperature and marked pain in the region of the bladder. Physical examination revealed no abnormality except evidence of recent loss of weight. The urine showed a trace of albumin, a few pus cells and the culture was sterile. The phthalein test showed an excretion of 45 per cent in two hours. On cystoscopic examination a definite hang on the wax bulb was obtained 5 cm. from the right ureteral orifice. A diagnosis of stricture of the right ureter with consequent back pressure on the right kidney was made. The patient continued to run an evening elevation of temperature up to 102 degrees. On July 14, cystoscopic examination revealed a bulging mass in the region of the left ureteral ridge, the surface of which was covered with necrotic slough. The orifice could not be seen. The mucous membrane around this mass was edematous. No evidence of tumor could be seen. On vaginal examination an extensive area of infiltration was felt in the region of the lower left ureter. The mass was quite hard and fixed to the surrounding structures. A diagnosis of carcinoma of the left ureter was then made.

On July 30, 1927, through an extraperitoneal incision, the stump of the left ureter was explored. A mass was found about 10 cm. in diameter extending down behind the bladder, entirely retroperitoneal, of rubbery consistency, which was firmly fixed to the surrounding tissues so that its removal was impossible.

Microscopic sections of the specimens (Fig. 15) removed at exploratory operation showed a rather necrotic looking stroma invaded everywhere by islands of proliferating squamous epithelial growth. The cells were large with vesicular nuclei, for the most part resembling somewhat the cells of a spinal-cell epithelioma. Other cells were still larger with dense masses of chromatin for nuclei. There were a

considerable number of mitotic figures. In view of the history (nephrectomy for hydronephrosis several years ago) and the site of the tumor, it is thought to have arisen from the ureter. Diagnosis: Squamous cell carcinoma (probably from the ureter).

From this time on her course was steadily down hill, with septic temperature, and the patient became irrational. Death finally occurred on October 21, 1927. No autopsy was obtained.

Comment.—This case presented unusual difficulty in early diagnosis on account of the fact that the catheter passed through the tumor. There was, however, free bleeding from this manipulation. The x-ray studies were also confusing in that dilatation of both ureters was present and no definite distortion or intra-ureteral filling defect was demonstrable. On operative exploration of the left kidney a marked hydronephrosis was found, but this condition was regarded as secondary to the stricture. It was six months later that marked obstruction in the lower left ureter was encountered. Again, in retrospect, I think a true appreciation of the situation should have been reached at this time on account of the obstruction in the ureter and the suspicious distortion of the cystogram. It was not, however, until two months later that a correct diagnosis was made when cystoscopic examination revealed a bulging mass in the region of the left ureteral ridge, but exploratory operation at this time revealed that the condition had become inoperable. Even had a correct diagnosis been reached at an earlier date, it is doubtful that the tumor could have been removed successfully as it proved to be of the squamous-cell type and it is, of course, well known that invasion of the wall of the ureter and involvement of the peri-ureteral structures occurs much earlier in squamous-cell carcinomata than in the more common papillary form.

In spite of the fact that primary tumors of the ureter are rare there are numerous reports in the literature and collections of cases. Rayer, in 1841, described the first case which was discovered at autopsy. Davy, in 1884, reported the first case in the English literature. Aschner, in 1922, collected forty-seven cases. R. L. Stewart, in 1926, collected five more cases and added one of his own. From a pathologic standpoint he divides the cases into sarcomata, which were found in five cases, benign papillomata, papillary carcinomata and nonpapillary carcinomata. Rousselot and Lamon, in 1930, reported a case of primary squamous-cell carcinoma of the

ureter and reviewed the literature up to this date, collecting forty-nine cases. In only fourteen was an accurate preoperative diagnosis made. The usual diagnosis was hydronephrosis, tumor of the kidney or renal or ureteral stone. The most common type of tumor was found to be a papillary carcinoma and only six squamous-cell tumors were encountered in the series. Stones occurred either in the kidney or in the ureter in six of the cases, which agrees with Albarran's findings of eight stones in fifty-three cases of epithelial tumors of the pelvis and ureter. Thirty patients died under treatment or a few months after leaving the hospital. Crance and Knickerbocker reported a case in which the patient was well two and a half years following operation.

A further review of the literature was carried out by McCown in 1930, who added a case of his own. In 1931, Renner again reviewed the literature and reported a most unusual case of a fibromyxochondro-carcinoma, in which a large tumor was excised from the bladder at suprapubic operation, the source of which was later found at autopsy to be an extensive tumor of the right ureter. He revised the statistics of Rousselot and Lamon and added the case of Player. In this series of forty-eight tumors he found that thirty-two arose from the lower third of the ureter, five from the mid-portion, and six from the upper third. In six cases the growth protruded into the bladder through the ureteral orifice. Papillary carcinomata occurred in nineteen cases (40 per cent), solid carcinoma in eleven cases (23 per cent), the squamous type in five cases (10.4 per cent), transitional cell tumor was diagnosed twice, and there was one instance each of cylindrical cell and adenocarcinoma. He reviewed the autopsy reports of the University of Vienna and found in 13,854 post-mortems three cases of primary ureteral carcinoma and one of ureteral myoma. Chauvin and Cerati were able to collect 108 cases in 1931 and added four. Calculus occurred in nine cases and leukoplakia in two. Papillomatous growths were most frequently encountered and they noted the rarity of metastatic deposits. Melicow and Findlay reported a multiple primary benign tumor of the ureter arising from an area of constriction below the uretero-pelvic juncture. On microscopic study these proved to be vascular fibrous polyps covered with layers of transitional epithelium. They reported seventeen additional cases of primary benign ureteral tumors from the literature. Spampinato, in 1932,

collected eighty-eight cases from the literature and added one of squamous-cell carcinoma involving the ureteral orifice, which was treated by nephro-ureterectomy and partial resection of the bladder.

From the cases which have been reviewed, and collected, it is evident that the vast majority of primary tumors of the ureter are of epithelial origin. The occurrence of sarcomata and myomata and of Renner's case, the description of which suggests a tumor of embryonic origin, is most unusual. The papillary tumors are most frequently encountered. Whether microscopically benign or malignant they tend, at least for a long time, to be limited to the lumen of the ureter and invade its wall only in the latest stages. They are extremely liable to implant themselves at different levels in the ureter or in the bladder, so that their differentiation into benign or malignant tumors is of pathologic interest only and has no bearing on the clinical management of the case. In the late stages they may invade the bladder wall and rarely lead to widespread metastasis.

Microscopically, the papillary tumors are characterized by villous processes, consisting of a thin stalk of connective tissue with nutrient blood vessels. These stalks are covered with a varying number of layers of transitional epithelial cells, as in bladder papillomata to which they bear a very close resemblance. Signs of malignancy are manifested by shortening and fusion of the villous processes with an increase of the layers of epithelial cells. The cells themselves become larger with irregular nuclei and karyokinetic figures. Invasion of the underlying fibrous tissue may become evident, but as has already been stated, it is only in the latest stages that the tumor cells invade the muscular coats of the ureter.

Squamous-cell epitheliomata are extremely rare. That they may arise as a result of long standing irritation from stones or infection seems certain and their relationship to leukoplakia cannot be denied. Patch, studying this question, reviewed the literature and found 121 cases of leukoplakia and 152 cases of squamous-cell carcinoma involving the kidneys, ureters and bladder. In thirteen cases there was a simultaneous occurrence of leukoplakia and squamous-cell carcinoma. He reported a case illustrating this relationship from his own observations. Squamous-cell carcinoma invades the ureteral wall comparatively early, extends into the peri-

ureteral tissues and leads to widespread metastasis as the case of Rousselot and Lamon demonstrates. In Spampinato's case there was rather extenive invasion of the bladder wall about the ureteral orifice.

Microscopically, one can see processes of typical squamous epithelial cells extending from the primary tumor and invading all coats of the ureter. A small nest of these cells may be seen in the lymph spaces. In the case which has been reported no definite epithelial pearls could be seen, and these have not been described in the few cases in the literature. Metastases occur first in the region of the retroperitoneal lymph glands and thence they spread through the internal organs.

A study of the literature emphasizes the difficulty in making an early diagnosis. The history is of little benefit. According to Stewart, hematuria occurs in 65 per cent of cases. Pain is a variable symptom. It is usually of a dull, aching character, referred from the kidney region, or may manifest itself as a typical ureteral colic due to obstruction in the ureter from a blood clot. Hydronephrosis occurs in 55 per cent of cases. According to the same author, it would seem that ureteral obstruction of at least some degree would occur in every case so that this percentage is probably low. Localizing symptoms aside from hematuria occur only when the tumor projects through the ureteral orifice into the bladder, when the bladder wall has been invaded, or when infection is present.

The general physical examination usually reveals nothing of value for early diagnosis. Quinby, however, has reported an advanced case in which a mass was palpable in the lower abdomen. An early diagnosis must be made by cystoscopic examination, ureteral catheterization and uretero-pyelography. In the few cases in which tumor can be seen projecting from the ureteral orifice, the diagnosis is simplified. On attempted ureteral catheterization, obstruction is usually met at the level of the tumor. When the catheter is withdrawn, free bleeding can be seen coming from the orifice. This finding has been described as the diagnostic syndrome of Chevassu and Mock. If the catheter can be introduced past the level of the tumor, clear urine will often be obtained from the kidney above, which tends to exclude the possibility of the kidney as the original source of the neoplasm. Plain x-rays are of little

value. They will often show, however, an enlargement of the kidney as a result of hydronephrosis. If functional tests can be carried out a variable amount of diminution of the functional ability of the kidney can usually be demonstrated. Pyelo-urterograms are often unsatisfactory, especially when the tumor occupies the lowermost portion of the ureter. They may, however, be of the utmost value, and conclusively prove the presence of neoplasm, as is illustrated in our first case.

All observers are agreed that when the diagnosis of ureteral tumor has been made, nephro-ureterectomy is the method of choice. Resection of the tumor-bearing area of the ureter with implantation of the proximal stump into the bladder has been advanced as a possibility to be considered in the treatment of a tumor low down in the ureter and of limited extent. Destruction of a small projecting tumor from the ureteral orifice by high frequency current has also been proposed, but these two procedures are mentioned simply to be condemned, or to be used in a case where the opposite kidney is missing. The very nature of the papillomatous growths, which make up the vast majority of ureteral tumors, makes it impossible to determine even from careful palpation of the outside of the ureter whether implantations have occurred along the extent of the ureter below the growth or, as a result of obstruction of the urinary stream, are present above. This possibility is well illustrated in Renner's case. The operation of nephro-ureterectomy is an extensive one and every precaution should be taken in the pre-operative care that the patient should be in the best possible condition. It is scarcely necessary to say that the functional integrity of the uninvolved kidney should be proven to be normal. The operative technic should be carried out according to the two-stage method of Marion. Gutierrez has fully reviewed the literature on nephro-ureterectomy.

It is a well recognized fact that implantation from papillary ureteral tumors or of those arising from the pelvis of the kidney may occur at any point throughout the course of the ureter, and there is in the museum of the Brady Urological Institute an instance of an implanattion which was found on pathologic examination involving the mucosa of the intramural portion of the ureter. It is, therefore, essential that in dealing with tumors of this nature the entire ureter should be removed with the kidney,

as the possibility of an implantation in the intramural portion cannot be disregarded. A simple division of the ureter as near the bladder as possible with cauterization and ligation of the distal stump, which is usually described as a complete ureterectomy, is not sufficient, as the mucosa in the intramural portion in such procedures is left intact and the possibility of implantations in this portion is disregarded. With good relaxation and exposure it is possible to resect a cuff of mucous membrane about the ureteral orifice, thus making the operation a complete one, but this procedure is often technically difficult, adding to the immediate danger of the operation, and may result in a persistent urinary fistula through breaking down of the resected area of bladder about the ureteral orifice. In dealing with these tumors the source of danger lies in the mucosa itself, as invasion of the muscular layers of the ureter does not occur in the early papillary implantations. A thorough destruction of the mucosa of the intramural portion of the ureter can be carried out easily by the high frequency current, and the operation may then be said to be ideal in that the kidney and ureter have been removed *in toto* with the exception of the distal stump, the mucosa of which has been completely destroyed.

Technic of Operation.—The lower ureter is exposed through the usual extraperitoneal muscle-splitting incision, roughly parallel with Poupart's ligament (Fig. *7*). If technically possible, especially in obese individuals, the introduction of a catheter into the ureter before operation will facilitate its recognition. However, this is usually not necessary as the tumor mass itself and dilated ureter make it easy to find. The ureter is then dissected from the retroperitoneal structures down to its entrance into the bladder and in an upward direction above the crest of the ilium (Fig. 6, *2* and *3*). Fixation of the surrounding tissue and the presence of enlarged glands would seem to indicate that the tumor has extended through the wall of the ureter, metastasis has already taken place, and that the case is inoperable. If, as is usually the case, the ureter can be satisfactorily freed, it is clamped with two clamps (Fig. 6, *4*), just above its entrance into the bladder and divided by the cutting cautery (Fig. *7*, *1*). The proximal stump is ligated with catgut, after thorough cauterization. Two clamps are placed on the edges of the distal stump (Fig. *7*, *2*) and the occluding

clamp is then removed. A high frequency electrode with a spherical tip is introduced into the lumen of the ureter (Fig. 7, *2*). The bipolar high frequency current is then turned on and the electrode passed up and down very slowly through the intramural portion of the ureter until the operator is certain that the mucosa has been completely destroyed. The distal stump is ligated with chromic catgut (Fig. 7, *3*) and the wound closed in layers in the usual way with drainage, care being taken to provide adequate drainage to the region of the stump. The patient is then turned on his side with the kidney elevator raised to afford good exposure by separating the crest of the ilium from the lower ribs. The usual lumbar incision is made, the muscles are divided, and the kidney exposed and separated from adhesions. The pelvis, which is usually dilated, is then isolated and the ureter dissected free from the surrounding retroperitoneal tissue until the portion of the ureter which had been dissected through the lower incision is reached. The ureter with the ligature on the lower end is then drawn out through the lumbar incision, the pedicle exposed, clamped and tied in the usual way, thus removing the kidney and ureter intact, with the knowledge that the entire mucosa in the stump has previously been destroyed.

SUMMARY

1. A case of primary papillary epithelioma of the ureter, with the hitherto unreported complication of implantation in a probably preëxisting bladder diverticulum, is reported.

2. The treatment consisted primarily of nephrectomy, followed by complete ureterectomy nine months later, when the correct diagnosis was made. Six months after the second operation, the diverticulum containing the tumor implant was removed.

3. The correct diagnosis was not made until persistent bleeding from the ureter was discovered by cystoscopic examination and the ureterogram presented a typical picture.

4. Two other cases from the records of the Brady Urological Institute, both resulting fatally, are reported.

5. The difficulties in early diagnosis are detailed. The value of the diagnostic syndrome of Chevassu and Mock—obstruction to the passage of a ureter catheter followed by copious flow of blood from the ureteral orifice—and the great importance of the ureterogram are emphasized.

6. A study of the pathology of ureteral tumors has been made and the conclusions shown to agree with those of previous authors on this subject reviewed from the literature.

7. That complete nephro-ureterectomy is the method of choice and should be employed in all cases where the condition of the patient will permit this operation, is the conclusion of all observers who have written on the subject.

8. The inadequacy of many methods of so-called complete nephro-ureterectomy is emphasized in that the mucous membrane of the distal stump of the ureter is not removed or destroyed.

9. The extreme importance of complete eradication or destruction of the entire ureteral mucous membrane, especially that in the intramural portion of the ureter where tumor implantation has been shown to occur, is emphasized.

10. A method of complete uretero-nephrectomy, combining the previously well known steps, but adding the hitherto unreported technic by which the mucous membrane of the distal stump of the ureter throughout its whole course through the bladder wall is completely destroyed by high frequency current, is reported.

I wish to express my gratitude to Dr. Hugh H. Young and Dr. William A. Frontz, of the Brady Urological Institute, through whose courtesy these cases have been reported.

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SOME DYSFUNCTIONS CAUSED BY NEOPLASM, ESPECIALLY OF THE ADRENAL GLAND

WILLIAM C. QUINBY, M.D.

From the Urological Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

Recent observations, pathologic, surgical and clinical, have drawn attention to the possible great significance of adenoma when such neoplastic structure is situated in one or other of the glands of internal secretion. In many such instances this form of tumor growth is associated with abnormalities of the most varied sort on the part of the endocrine and autonomic nervous system. Further it has even more recently been shown, in the case of the pancreas and parathyroid at least, that the removal of such an adenoma may be followed by a return of the patient to normal. Therefore, a consideration of such knowledge as we have concerning these growths and their effects seems timely.

The adenoma is described by Ewing as "an organoid tumor which reproduces the structure of a gland." A complete and typical adenoma reproduces epithelial alveoli, gland ducts, membrana propria, stroma and vessels in a somewhat orderly and functionating organ as in mamma and thyroid. More atypical adenomas are devoid of definite function.

In gross appearance the adenomas are usually well circumscribed or encapsulated tumors, which do not infiltrate the surrounding tissue, as do carcinomas. Clinically true adenomas are usually slow of development and of limited growth capacity. Their disturbance of the organism is chiefly mechanical. Functional capacity is retained by many adenomas. Occasionally it is much increased and probably in all cases the product is abnormal.

When one considers the great variety of conditions in which an adenomatous morphology is presented and analyzes their physiologic and clinical significance, the conclusion must be reached that adenoma is rarely a distinct morphologic entity, but is rather to be regarded as a series of structures which tissues assume in response to various forms of irritation, functional activity and overgrowth.

It is chiefly, if not exclusively, the adenomas of embryonal origin which fail to show this complex significance. It were better, therefore, in most instances to avoid the rigid morphologic conception of adenoma and to regard the diseases marked by adenomatous hyperplasia as specific clinical and pathologic entities. Thus some adenomas are traceable to a localized inflammatory overgrowth. Others represent chiefly an excessive response to functional stimulus. Some appear to owe their existence to minor anatomic disturbances in the blood supply, or to configuration of the organ. Many true adenomas represent pronounced neoplastic growth of definitely misplaced and embryonal portions of gland tissue. Probably more than one of these factors may be combined in origin of the same adenoma.

Later, as examples of functional adenomatoid hyperplasia, Ewing refers to those of the breast, the thyroid, the hypophysis and the adrenal gland.

There seems little doubt, therefore, that due to stimuli frequently as yet only to be surmised, several, if not all of the endocrine glands may show hyperplasia, and that this hyperplasia may be found to have taken on an adenomatous form or, even at a later period, to have undergone transformation into true carcinoma.

For the clinician, the important fact is that such adenomas are able to call forth functional activity of the gland in which they occur, though such function is often abnormal and perverted, so that by its action the normal physico-chemical balance between the various endocrine organs of the body is strikingly upset.

Cushing in his Lister Lecture states the situation at present as follows:

". . . the adenomas of the secretory organs, once regarded merely as curiosities of morbid anatomy, but now shown to be functionally active conglomerations of cells which may disastrously upset the physico-chemical balance of the body. Through their hypersecretory effects they lead to recognizable states, the contrary of those expressions of glandular inactivity seen in myxedema, tetany, diabetes mellitus, or Addisonism. One after another they are coming to be recognized. The relation of the thyroid adenomas to hyperthyroidism was first brought to our attention. Then came the knowledge that the adenoma of acromegaly caused its effects by an excess of a normal secretion rather than by some abnormal secretory product as had been surmised. In its turn the association of hypertension with suprarenal tumors, particularly those composed of chromaffine medullary

cells, began to be looked upon as the symptomatic verso of Addison's disease. Then the syndrome of hyperparathyroidism (osteomalacia with muscular hypotonia, multiple bone tumors and abnormal excretion of calcium) due to a predictable adenoma of one of the parathyroid glandules was in its turn disclosed. And on the heels of this discovery the conjecture that certain clinical states, which bear a symptomatic resemblance to the effects of overdosage with insulin, might be due to an adenomatous hypersecretion of the pancreatic islets has become an established fact. . . . and to these known hypersecretory syndromes may now be added that caused by a pituitary adenoma of basophile elements."

As urologists we are interested especially with instances in which these various manifestations include also changes in the normal sexual sphere. Here the question as to whether the stimulation of the gonadal function is due to faulty action of the pituitary or of the adrenal gland is important. It has been pointed out that in acromegaly one finds hyperplasia of the adrenal gland and sexual dysfunction (amenorrhea and impotence) though this is a disease surely of pituitary and not adrenal origin. This whole subject is still but imperfectly understood. On the whole, however, the various disorders of the pituitary gland affect the sexual sphere by inhibition rather than by stimulation. As an instance of the stimulating effect of an adenoma of the adrenal gland the following case is described.

CASE REPORT

The patient was a boy, twelve years of age. He was born January 19, 1919, was at first breast fed, then weaned, and made satisfactory progress with no abnormal manifestations till November, 1919, when it was noted that his voice was becoming deep, and that there was a beginning growth of public hair. A month later it was evident from the size of the external genitalia together with the increase in hirsutes that precocious puberty was appearing. He was given extract of the pineal gland which he took more or less consistently during the ensuing ten years.

In December, 1919, the adenoids were removed.

In May, 1920, sixteen months of age, he was 34.5 inches tall and weighed 31.5 pounds. The circumference of the head was 20¼ inches and the chest 21 inches. He was walking, saying a few words and had sixteen teeth.

In May, 1921, his tonsils were removed. He was gaining weight rather rapidly.

At the age of five years and four months he was 48.5 inches tall

and weighed 53¾ pounds. The external genitalia were fully developed and pubic and axillary hair was present.

In the fall of 1930 the boy had developed to the point where he weighed 140.5 pounds and was 64.5 inches tall. He was unusually alert mentally and took active interest in all forms of athletic sports. His general appearance, both mentally as well as physically, was that of a boy of about sixteen or seventeen years of age. During the past year or so he had been showing definite beard on lip and chin and

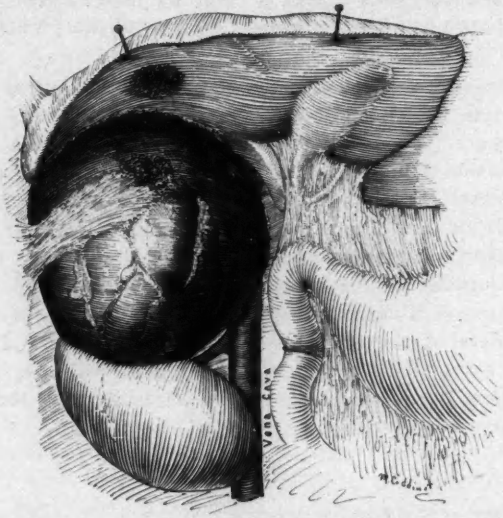

Fig. 1. Sketch of anatomic relations of tumor. Note that there is no infiltration of the kidney. On lifting the right lobe of the liver, the area of rupture of the tumor which resulted in intra-abdominal hemorrhage is seen.

more recently had been having a rather widely distributed acne on face, brow, shoulders and back. The skin appeared, in general, oily and roughened. At this time it was found that the blood pressure was 152/90 and the blood sugar was 108 mg. per cent. The N.P.N. was 31 mg. per cent. There were no abnormal areas of pigmentation and no abnormal masses were to be felt in the abdomen. His scholastic ability was outstanding.

Such was the condition of affairs on December 5, 1930, when the following occurrence took place. An hour and a half after his lunch, which was a hearty one, he ran several laps on a track. About 4 o'clock he felt rather mean and lay down, and began to have crampy

abdominal pain. This persisted. He went home about 5:30 p. m. His bowels moved. He lay down; the pain was perhaps a little better. About 7 p. m. he had another bowel movement and at this time he became very faint, sweated, desired to drink, and appeared, to his father, abnormally pale with a slow pulse. When seen by his physician his pulse was 76; temperature 98.4°; the abdomen decidedly full, rather tense and tympanitic. He had passed no gas except a little with his bowel movement. Only general abdominal tenderness with more notable resistance in the epigastrium on the right was found. The local spasm and tenderness in the abdomen increased. Rectal examination was negative.

In view of the history and physical development, which suggested the possibility of a cerebral or adrenal growth causing precocity, the possibility of adrenal tumor which had ruptured into the abdominal cavity was considered, but in view of the white count of 29,000 the possibility of a ruptured viscus was considered far more probable. There was also kept in mind the possibility of there being present an intestinal reaction to some vasomotor disturbance. An exploratory operation was undertaken forthwith.

Incision was made through the upper right rectus at about its midpoint. On opening the peritoneum, a blood clot at once pushed up and the abdomen was found to contain probably a quart of dark blood. Examination of the left lateral fossa was negative. Examination of the right fossa showed it to be filled with a large retroperitoneal tumor, of which the median portion extended to the midline close to the liver. Examination caused so much straining that it was unwise to explore further and no evidence of an opening in the surface of the tumor was found. After letting out a good deal of blood the abdomen was closed.

Laboratory Data.—Before operation—urine acid, 1.030; no albumin or sugar. Sediment negative. White blood cells, 29,000; red cells, 5,000,000. Blood pressure, 162/65. Temperature normal; pulse, 100-110; respirations, 20.

The next day the patient's condition was satisfactory; the temperature being normal and the pulse rate only about 100. Blood pressure had remained at about 150/80.

During the following sixteen days the boy made a normal recovery from the exploratory operation to the point where the wound was well healed and the appetite and bowels normal, except that rather frequent enemata were needed to relieve distention. Repeated examinations of the blood showed the white cells varying between 16,000 and 20,000; the red cells from 5,000,000 to 5,600,000 and the hemoglobin from 80 to 90 per cent. The systolic blood pressure showed a steady slow rise from a reading of about 140 at the time of operation to about 170 two weeks later. A week after operation sugar ap-

peared in the urine, ranging in the next week as high as 6 grams in twenty-four hours.

X-ray examination showed a soft tissue mass in the right lumbar region and the outline of the right kidney could not be made out. Irregular scattered areas of increased density appeared in the region

Fig. 2. A sagittal section of the tumor and liver to show the character of invasion. Note that extensive remains of a well defined capsule can still be seen. Note also the intimate relation of the growth to the diaphragm and pleura.

of the tenth and eleventh ribs on the right. The shadow of a circular mass of calcification was seen about 6 cm. in diameter just internal and below these. So far as seen the lungs appeared clear.

On the seventeenth day after the first operation, an exploration of the upper right side of the abdomen was undertaken, the pre-operative diagnosis being that of an adrenal cortical neoplasm which had caused intra-abdominal hemorrhage. The operative note was as follows:

"Patient undoubtedly has neoplasm of the adrenal gland, probably arising from the cortical tissue. In the effused blood removed at the previous operation, cells identical with this organ were found. Arrangements for continuous intravenous saline were made. The region of the right kidney and suprarenal gland were exposed by an incision following the margin of the ribs on the right, beginning at the ensiform and swinging downward as far as the lumbar muscles. Through this the peritoneum as well as the renal fossa were opened. There presented first the hepatic flexure of the colon which, after a slight amount of dissection, was dislocated downward and toward the midline. There then came in view a large mass which was felt at first to be liver but which on more careful inspection was found to be neoplasm. This filled the whole right hypochondrium, pushing the kidney downward to the level of the iliac crest and pushing the liver upward and toward the midline so that in the operative incision at the beginning only a small margin of right lobe was to be seen. On lifting up this right lobe of the liver, the source of the original hemorrhage became apparent in an area on the anterior surface of the tumor which was necrotic and adherent to the liver, the tumor having broken through the parietal peritoneum at this point. Investigation of the relation between the tumor and the kidney showed that there was no union of the two structures and that the tumor could be enucleated easily from above the kidney. The tumor was very large and very tense, but careful palpation showed that it was slightly fluctant. Because of its size, it was entirely impossible to investigate the anatomic conditions toward the midline of the body. Therefore, the ninth and tenth ribs and the eighth rib cartilage were incised after removing the periosteum, and broken outward so that by this means still further access to the field of operation was gained. Still, however, it was impossible to approach the vascular side of the tumor mass, so that a reduction in the size of the tumor seemed to be imperative. Using the endothermy knife, an incision about 3 inches long was made on the anterior aspect of the tumor through its capsule, and a large amount of necrotic soft tumor mass found. This was removed by the endothermy loop and suction tube until a cavity larger than a fist had been produced. During this procedure there was a moderate amount of bleeding which was controlled wherever it seemed to be severe by the endothermy current and by packing. The upper limits of the cavity which had been produced seemed to encroach more and more on viable tissue. Sufficient mobility of the tumor mass was produced by this method so that an investigation of the vascular supply could be undertaken. The renal vein which ran along the mesial aspect of the lower pole of the tumor was carefully dissected away from the neoplasm and the cava reached. Here there were found a few venous connections between this large vessel and the tumor, but they were of small size and could be easily tied between

clamps. After a careful and somewhat tedious dissection it was finally possible to isolate the tumor entirely from the vena cava. In one spot the tumor mass was found surrounding the cava, running underneath it, but this portion was freed without untoward event. Thus the tumor was freed throughout its lower half. There still remained adhesion between the tumor and the under surface of the liver. An attempt to investigate this region from the anterior aspect of the tumor was met immediately by sharp bleeding so that these areas had to be packed temporarily.

"The whole operation, from the beginning, was attended with an unusual amount of hemorrhage and capillary oozing, undoubtedly due to the increased vascularity of all the tissues in the neighborhood of the growth. The boy's condition had been satisfactory up to this point and in fact was so still, but it seemed sure that a further attempt to deliver the tumor from the liver would be attended with a considerable loss of blood, so that it was deemed wise to finish the operation at this point. Throughout the operation no definite evidence of metastases had been found. There was a small nodule found on the peritoneal aspect of the colon, early in the operation, which was reported by the pathologist to be merely fat. On the extreme edge of the liver there was also a small miliary spot which was dissected out, but on which pathologic report had not been returned at this time. Although, without any doubt, the tumor was growing outside its capsule and was locally invasive, there had been no evidence obtained that it could not eventually be enucleated. It seemed wise, therefore, to make a two-stage attempt; so that the wound was now closed. This was done with deep through-and-through stitches of silkworm gut in several places, pulling the elevated rib margin down into place, after which the rest of the wound was closed as usual, a thin rubber tissue being interposed between the tumor and the cava, and the cavity which had been made in the tumor being packed with gauze. Considering the severity of the operation, the patient's condition at the end was fairly satisfactory.

"Following this operation, in spite of continuous intravenous cylsis of saline and adrenalin during operation, and two whole blood transfusions afterwards, the patient's pulse steadily rose while the blood pressure fell. Death occurred about twelve hours after operation."

The pathologic report was as follows:

Microscopic Report.—"These are sections of a highly cellular tumor whose supporting stroma and architecture is dependent upon thin-walled, slit-like blood vessels and sinusoids. The parallel vascular channels and sinusoids divide the tumor into cords and sheets of varying sizes. Portions of the tumor are granular, eosin staining with complete loss of cytological detail. Similar changes, though less extensive, occur in the central portions of broader cords, whereas, the cells adjacent to the blood vessels are well preserved. In the better

preserved portions the cords are from three to six cells in width and simulate the fascicular zone of the adrenal cortex. The cells are somewhat poorly defined, oval to polyhedral in shape with an eosinophilic, finely granulated cytoplasm and large oval granular to fascicular nucleus and prominent nucleolus. Cells with hyperchromatic nuclei are numerous. Cells in mitoses are few to moderate in number, have coarse, irregular, widely separated masses of chromatin. Multiple mitoses with two and, rarely, three spindles are seen. Multinucleated cells with irregular sized and arranged nuclei are present in small numbers in the more rapidly growing portions of the tumor. Rarely a cell contains lipoid in its cytoplasm as most of the cells have the finely granular eosin cytoplasm already described.

"We are thus dealing with a tumor of adrenal cortex origin, showing evidence of moderately rapid growth with areas of degeneration and invasion of the liver. It, therefore, should be considered as an adrenal carcinoma with extension to liver and of malignant character."

This case, then, is a striking illustration of the effects of an adrenal neoplasm in causing precocious puberty together with abnormalities associated with the appendages of the skin such as hypersecretion of the oil glands, elevation of the blood pressure, leukocytosis which may well have been a terminal effect, and, toward the end, glycosuria. Whether or not the tumor was originally an adenoma must, of course, remain in doubt, but that it was of long duration is demonstrated by the considerable amount of calcification as seen by x-ray: Pathologic examination shows evidence still remaining of a definite capsule, and it is highly probable that we have here to do with an adrenal cortical tumor of adenomatous character during many years, which finally, taking on malignant changes, became invasive and caused the clinical picture and events above described.

The lesson is evident: In view of our present knowledge of the dysfunctions of glands of the endocrine system, when such are found to occur, the patient should be given the benefit of any exploratory operation which may seem indicated, whether it be directed toward the thyroid or parathyroid, the pancreas, the adrenal or even the pituitary gland, in the hope that an adenoma may be found, removal of which will be followed by cure.

DISCUSSION

DR. HUGH H. YOUNG (Baltimore, Md.): Dr. Quinby's paper has interested me very much, because it seems to me that the next advance in urology is going to be in the pathology and surgery of the adrenal glands. As yet we know very little about the adrenals and the treatment of conditions which arise from adrenal pathology is largely a *terra incognita,* as it is in regard to other glands of internal secretion. But, as Dr. Quinby says, there is gradually accumulating in the literature, cases of great interest, which will undoubtedly affect the future of adrenal surgery, and broaden the field of urology as time goes on.

The case I am to report is interesting. About two or three weeks ago, an infant three and one-half years old appeared in the children's department at Johns Hopkins Hospital. He was about 4 feet high and weighed 62 pounds. A careful study with the x-ray showed nothing in the region of the pituitary gland. There was nothing definitely palpable in the abdomen.

There was very marked development of male genitalia, certainly those of a sturdy adult. A very careful study showed there was a well developed prostate, and massage of the seminal vesicle brought forth spermatoza. He had frequent erections, very large ones, and gave evidence of sexual desire. I firmly believe he could have carried out his part in coitus. He had a bass voice and proudly admitted "he had a girl." He might have even become a father only three and a half years older than his son. I was anxious to mate him, but found no takers.

Both medical and urologic consultants were agreed that the adrenal glands would probably be found abnormal, and we decided to make an abdominal incision to examine each adrenal gland by palpation. As the literature contained very little of assistance, studies were made with the help of Dr. Lloyd Lewis to determine the simplest and most satisfactory method of palpating the adrenal glands through an abdominal incision.

The method which was finally evolved comprised a high midline incision, beginning at the ensiform and extending downward about 5 inches. After separating the recti muscles, the peritoneum

was opened, disclosing the liver on the right side and the stomach below and to the left. To reach the left adrenal gland, the hand should be introduced above the stomach and beneath the liver and directed downward and to the left, eventually palpating the upper end of the kidney and the adrenal gland immediately above it. On the right side, the left hand would be employed and pass beneath the under surface of the liver, external to the gall bladder until the kidney is palpated. Following inward from that point, the adrenal gland was easily found. It was not necessary to introduce the thumb on either side in infants or thin adults.

Employing this method in our remarkable young patient, we discovered that the left adrenal gland was a little larger than normal, but the right adrenal seemed smaller than normal, and difficult to outline exactly. After consultation with others present, there seemed nothing to be done.

There is no more interesting field in urology than the diseases and surgery of the adrenal glands, which is as yet in its infancy.

DR. E. G. CRABTREE (Boston, Mass.): In the discussion of Dr. Fowler's case of primary carcinoma of the ureter, I want to report a case of very short duration of symptoms and of very minor degree of involvement of the ureter in primary carcinoma. This man, similar to his case, was sixty-one. Fortunately for us, he had been in the hospital just a year previous for a thorough overhauling because of cardiac and glycosuria conditions. During that stay in the hospital, sixteen urinary examinations were made, all of which were entirely negative. He then returned to the hospital a year later with hematuria. The rest of the data was negative, except for his cardiac condition which was angina in type and the fact that he had a bad glycosuria which was kept under control.

The accompanying pictures illustrate the type of lesion which he had.

His functions were excellent on his normal side and only a trace of color on the other, although the ureter was marked. The obstruction (Fig. 1) was in this region, the lower third of the ureter, and was irregular in character. The ureter catheter would not pass by. The remainder of the ureter was normal. The degree of dilatation of the kidney pelvis was not large, although the degree of the obstruction was pronounced.

Operation was done after two or three confirmatory pyelographies were made but the diagnosis was not clean-cut. The similarity, from the irregular ureterograms, to the papillary overgrowth

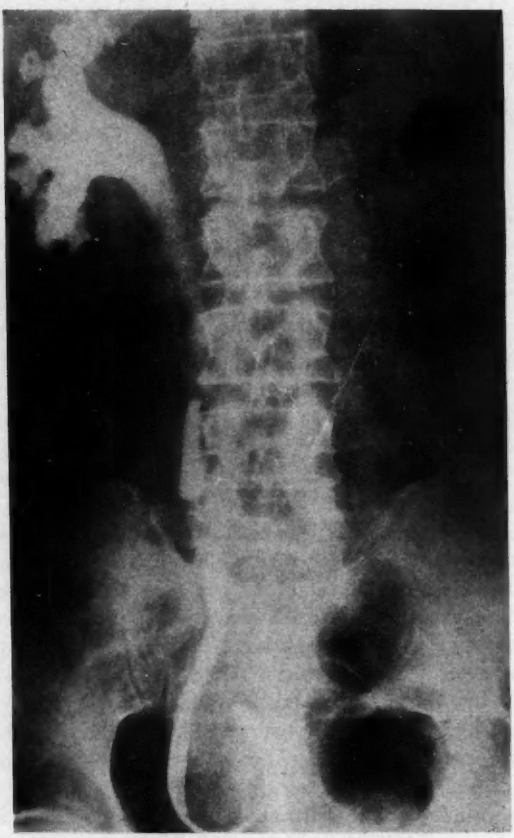

Fig. 1. The pyelo-ureterogram on which the diagnosis of ragged ureter deformity was made.

of epithelium, non-malginant in character, was apparent. A differential diagnosis was not made.

Figure 2 shows the specimen which was removed. At the time

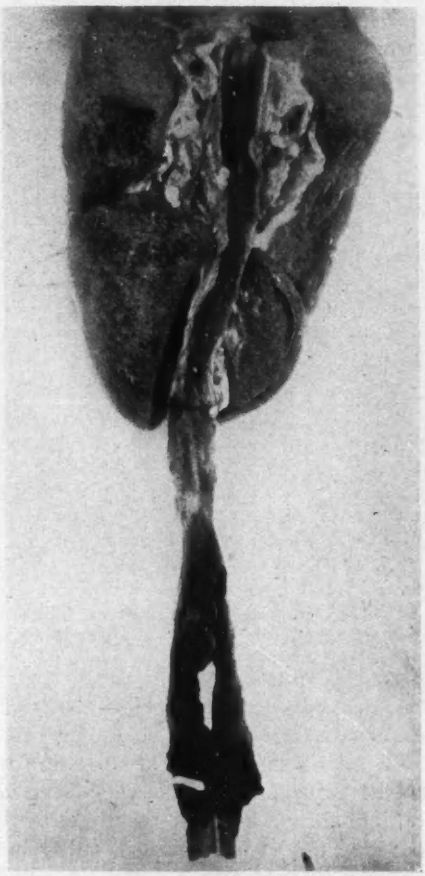

Fig. 2. The photograph of the specimen removed at operation. The opening in the center is the site of the frozen section taken at the operation table.

of operation, the character of this growth could not be determined by palpation. At one time, it was thought to be a stone, at another time it was thought to be a stricture. This small opening here was made for excision of a piece of the tumor. The frozen section showed it to be malignant.

The only thing in the physical examination which was unusual was that the patient was fuller than normal in the right side, fuller than the pyelogram explained. There was no tenderness.

Fig. 3. The low power section at the very extreme lower edge of the carcinoma where it joins the normal ureteral wall. There is distinct papillary tendency shown here.

The operation done was to excise below the tumor so that the piece of the ureter was removed. The kidney itself was apparently normal. An interesting finding at operation was induration of the fat about the kidney, which was very large in amount, and very much more than normal in amount. Pieces of this fatty tissue were taken and found not to be abnormal, either in the nature of the fibrous capsule or in the nature of the fat within the lobules.

Figure 3 shows the junction of the tumor and the normal ureteral wall—the ureteral wall at this point shows normal tissue. Above this area appears the papillary overgrowth type of tumor. Pathologically, it was invading carcinoma. Tumor-cell invasion did not involve the serosa. The mucosa was quite extensively in-

volved. There was no adherence of the ureter to the peri-ureteral tissues. It was very similar to a fibrous mass when seen from the outside, and only through frozen section made at the operating table could the diagnosis of malignancy be established.

Figure 4 is a microphotograph which is confirmatory of the diagnosis of carcinoma.

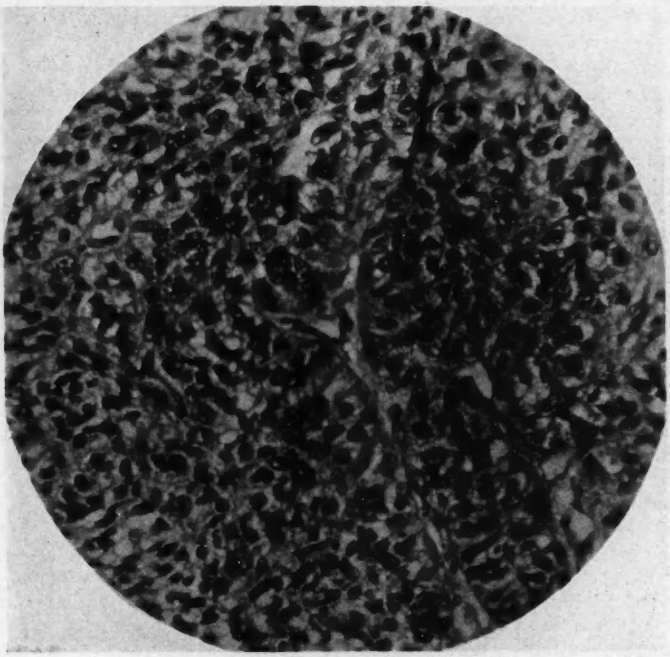

Fig. 4. A high power view through the main portion of the carcinoma.

CASE REPORT

Mr. L. W., aged sixty-one years, had been under treatment for diabetes for seventeen years. He had been studied thoroughly in the hospital, and one year ago was discharged sugar-free with a normal blood sugar maintained on a diet of 50 grams of carbohydrate, 80 grams of protein and 120 grams of fat. During this admission to the hospital, seventeen urine examinations had been done, all of which were negative except for the sugar reaction.

Blood Wassermann, N. P. N., white cell count, red cell count and blood smear were all negative. He was in good flesh and apparently in excellent condition except for his sugar.

For the past few months there had been cardiac symptoms with attacks of angina. Ten days before admission to the hospital the patient had attacks of slight degree of pain in the right back accompanied by hematuria. There had been some discomfort in the perineum during the period of bleeding, but this disappeared after the first few days. His cardiac condition had been giving little trouble in the last few weeks.

Physical examination showed cardiac sclerosis and angina. The patient was apparently in good condition, showing no loss of weight with his heart compensated. Neither kidney was palpable. There were no masses in the abdomen. There was, however, a sense of fullness in the right loin associated with dullness to percussion.

Urine examination, on admission, showed a small trace of albumin, no sugar, and the sediment contained ten to fifteen red cells. The prostate was moderately enlarged from a benign adenoma, but there was no residual urine.

Cystoscopic examination showed a normal size urethra; the bladder appeared to be normal; both ureters were easily seen. The left ureter catheter passed readily to the pelvis without meeting obstruction, drawing clear urine with an appearance time of three minutes and a 20 per cent function with phthalein. Microscopic sediment of the left urine was negative. The right ureter was obstructed about 3 inches above the bladder. The right urine was bloody and the sediment contained gross blood. There was no function obtained from this side, although a small degree may have been masked by the amount of blood.

Bilateral pyelography was done which showed a normal left kidney and ureter. The outline of the right kidney was obscured by gas. The right renal pelvis incompletely filled and the right ureterogram showed evidence of obstruction at the level of the fifth lumbar vertebra, but was indefinite in character. These films were inadequate for diagnosis, and the right pyelo-ureterogram was repeated three days later. The obstruction to the right ureter was still present in the same location. This area of the ureter showed a very irregular filling defect, about one and one-eighth inch in length at the level of the fifth lumbar vertebra and the lumen through this area was very irregular indeed.

It seemed unlikely that the lesion could be either a stone or a stricture, although papillary ureteritis was possible.

Operation was advised and performed. Mid-ureter was exposed through a low loin incision in the position indicated by the pyelograph, just below the brim of the pelvis. The ureter was thickened and firm, although not adherent to the surrounding tissue. Hardness was

about that commonly encountered in calculus, although it was general and no discrete area could be felt. The amount of induration was way beyond normal for stricture of the ureter. A section was removed for diagnosis which showed malignancy. The ureter was then severed below the tumor growth. The incision was enlarged upward in order that a nephrectomy might be accomplished. On approaching the renal bed the kidney was found to be surrounded by dense, lobulated masses of perirenal fat which was harder than normal to palpation with a tendency to a definite lobulation similar to a lipoma. Some of this fat was removed for pathologic examination. A nephrectomy was done.

Pathological Report.—The specimen consisted of two portions, one a kidney with the attached ureter, the other several nodules of fatty tissue. The kidney attached 15 cm. of its ureter. The ureter was 3 mm. in diameter. There was an area 2 cm. long and 1.5 cm. wide with papillary projections in the lumen of the ureter. The tissue was firm to palpation. There was nothing remarkable about the kidney itself. Microscopic sections of the ureter showed a mucosa of pseudostratified squamous epithelium. This was resting on a smooth basement membrane. Some areas showed the cells to be heaped up and to be growing deeper into the tissue below the membrane. The loose areolar tissue below the basement membrane was vascular and in places contained many round cells. Areas were present in which there were small masses of tumor cells. The cells were epithelial in type, had a definite cell membrane and a vesicular cytoplasm. The nuclei were large, many of them showing mitotic figures. The muscularis, for the most part, was normal but had areas in which these tumor cells had invaded. The serosa was thick, vascular and contained numerous lymphocytes. No definite tumor cells were seen in the serosa. A section below the tumor showed no invasion of tissue and the ureter had some evidence of chronic inflammation. Sections of the fat around the kidney showed no increase of fibrous tissue. The fat cells were all adult fat cells. There was nothing to suggest an abnormal proliferation of the interlobar fibrous tissue septa.

Diagnosis: Carcinoma of the ureter.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): Considerable progress has been made in recent years in our methods of diagnosis of tumors of the ureter so that they are being reported in increasing numbers. That they are not always easy to diagnose, however, is shown by the fact that in our series of tumors of the ureter, the kidney had been removed elsewhere in two instances for hematuria which persisted after operation, and on clinical examination we found the tumor of the ureter.

The methods of diagnosis will be variable. In the first place,

cystoscopic inspection of the affected ureteral orifice may be of value. Since most tumors of the ureter are in the lower third of the ureter, the hematuria will often be of an oozing type and quite different from that observed when of renal origin. When the tumor is situated near the intramural portion, a continuous dribble of hemorrhagic urine is often observed. On introducing a ureteral catheter into the lower third of the ureter, the collected urine is often bloody and when the catheter is introduced higher, the urine will become clear.

In several cases, I have removed tissue by means of small forceps inserted into the ureter, which permitted diagnosis from the microscopic findings.

Urography should enable us to recognize the lesion better than any other single method. Intravenous urography has, in my experience, not proved to be as helpful as the retrograde method. The deformity usually observed consists either of a filling defect, localized ureterectasis or sacculation, and a variable degree of pyelectasis.

The Broders classification is undoubtedly of much value in determining the prognosis with tumors of the ureter.

It is not always easy to differentiate a primary tumor of the ureter from one of metastatic origin. I recently observed a patient with a very large tumor in the lower third of the ureter, which was apparently a primary tumor. The urogram showed an extensive filling defect in the lower ureter, localized ureterectasis, and a normal pelvic outline. However, on surgical inspection of the kidney, a primary tumor was found in the renal pelvis, which was not more than 1.5 cm. in diameter. The tumor had caused no renal symptoms whatever, the patient complaining only of painless hematuria. It was of interest that the secondary metastasis in the lower ureter was five or six times as large as the primary tumor in the kidney.

From the surgical standpoint, the importance of thorough resection of that portion of the bladder which is adjacent to the ureteral orifice should be emphasized. This has been described both by Dr. Judd and Dr. Hunt in previous papers.

Dr. Henry G. Bugbee (New York City): I would like to cite an instance of an adrenal tumor in a woman who has been under observation for the past few months. She came to the hospital stat-

ing that she had noticed a lump in her abdomen and was suffering from pain.

She was twenty-eight years of age, had not menstruated for three years, had a growth of hair several inches long over her chest and abdomen. Her heart action was rapid, and she was exceedingly nervous. A mass could be felt in her left upper abdomen which extended below the ribs and even tended to push out the ribs. The mass could be palpated posteriorly, but was more prominent anteriorly. Examination of her urinary tract was negative. The left kidney showed normal function. The outline of the pelvis and calices was normal; the kidney, however, was pushed down by this mass. X-rays showed metastasis in the lung. Therefore, no operation was carried out.

Dr. Braasch saw this woman while in New York this winter, and concurred in our advice that we should not attempt to remove the growth inasmuch as metastases were present. She has had deep x-ray therapy; the mass has receded about two-thirds and she has been relieved of her pain.

Dr. Roger C. Graves (Boston, Mass.): I am convinced by this discussion of tumors of the ureter that we must do the operation of nephro-ureterectomy more often than we have in the past, when there is pathology sufficient to require nephrectomy as far as the kidney is concerned, and when there is at the same time a stricture of the lower end of the ureter, whether due to tumor or to tuberculosis or to advanced infection. Beer has emphasized these indications. I do not believe that the complete operation adds very greatly to the hazard in most cases. Certainly the disadvantages will not offset the advantages in removing the whole ureter under such circumstances, because if we tie off the upper end of the ureteral stump and leave the lower end completely strictured, we apparently must expect, in some instances, the unchecked growth of an unrecognized tumor or the continuance of pain because of a distended ureteral stump or the gradual development of a pyo-ureter.

I feel that Dr. Colston has made a very excellent suggestion with reference to the treatment of the intramural segment of the ureter in the technic of ureterectomy. The removal of that segment is the most difficult part of the operation and it does add more to the time and the hazard than any other part of it. The possibility of

coagulating this portion with an electrode put through it into the bladder and then gradually drawn out through the stump is a very interesting one and worth a trial. One should leave a drain in that region, however, to provide for any leakage that might later take place.

Dr. J. Bentley Squier (New York City): I would like to add one case of adrenal tumor which has been in our clinic. It is very comparable to the one Dr. Bugbee presented. However, when the woman came to the hospital, she had a deep bass voice, hair on the face which she shaved every day, and all the other characteristics that very often go with an adrenal neoplasm. The diagnosis was made by one of the residents on the medical service. She was sent to us and we went over her very carefully and found a large adrenal tumor with no metastases elsewhere in the body which were demonstrable by an x-ray examination. Dr. Cahill, my associate, did a transperitoneal operation and removed this tumor. The woman left the hospital with a soprano voice, with cessation of the growth of hair on her face. The change was remarkable.

One year later, she returned with a recurrence of all her objective symptoms. The deep voice had come back, the hair had returned on her face and other manifestations of adrenal tumor. At this time x-ray revealed multiple metastasis in the lungs. There was no recurrence at the site of operation. She died and a complete autopsy was done and there was found a very general metastasis scattered throughout her body. I simply refer to the case as another one for the record.

Dr. Richard F. O'Neil (Boston, Mass.): I would like to add another case of primary tumor of the ureter in which I plead guilty to having done a nephrectomy without realizing the diagnosis. The patient was not my own, but one that I inherited while Dr. Chute was away. She had a very severe arthritis and for some reason her urinary tract had been investigated and there was an obstruction in the right ureter which could not be catheterized. When I saw her, she had temperature and tenderness in the right flank and all the signs of a shut off kidney. We decided a nephrectomy was necessary. This was done and we found a tense renal pelvis filled with dark colored fluid. I did not feel any obstruction in the ureter as it was evidently considerably lower down.

She made a good recovery from the operation. Her temperature dropped. She died two months later from some other cause and autopsy showed primary carcinoma of the ureter with no metastases.

DR. J. BENTLEY SQUIER (New York City): I would like to add one word regarding the tumor of the lower end of the ureter, especially the lower third. I wonder if Dr. Braasch, in his very large experience, has seen in making cystograms of these people that the filling defect in the bladder is almost invariably a conical retraction towards the ureter where the tumor is. It is a characteristic filling defect as against the filling defects found in tuberculosis and in inflammatory conditions.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): That is a very interesting point which Dr. Squier has brought up. It has been my observation that if there is pathology in the ureter of any kind, there will often be conical deformity of the bladder wall in the cystogram, with the apex toward the affected ureter.

DR. H. A. FOWLER (Washington, D. C.): All I have to add is the fact, which I did not state, that the pathology in the case reported by me was that of a squamous-cell carcinoma. This had involved the mucosa, which became ulcerated. The abdomen was entirely filled with the tumor mass which had invaded the liver extensively.

DR. J. A. C. COLSTON (Baltimore, Md.): I was very glad to hear Dr. Fowler state that his case was one of squamous-cell carcinoma. It is well known that this variety is much more dangerous in that it infiltrates the bladder wall early and may lead to early metastasis in the regional lymph nodes. These properties are in distinct contrast to the more frequent type of ureteral tumor; that is, the papillary epitheliomas in which it is well recognized that the tumor spreads by implantation in the mucosa. Therefore, the method of treatment which I have described is particularly fitted for dealing with the papillary epitheliomata because, by a simple technic, the entire mucosa, which is the source of danger in these cases, can be readily destroyed. The operation of resection of a cuff of bladder mucosa about the ureteral orifice, which Dr. Braasch has mentioned, should be reserved for cases of squamous-cell epi-

thelioma with obvious involvement of the orifice itself. In dealing with papillary epitheliomata, the resection of a cuff of bladder mucosa around the orifice is unnecessary, offers more opportunity for implantation and certainly increases the danger of operation.

In closing, I should like to pay a tribute to the courage, coöperation and resisting powers of this patient, who successfully withstood three major operations at my hands.

Dr. William C. Quinby (Boston, Mass.): It has been very gratifying, gentlemen, to have you so brilliantly discuss this question of hypergenitalism due to the adrenal gland. Dr. Young's patient is absolutely a case in point. The efforts which were made to find out something about the adrenal gland were most interesting. The problem is hard because the adrenal gland is of much larger size in relation to that of the kidney during early life, shortly after birth, but it assumes practically its normal relationship at about one year of age.

I would suggest that we probably will find that the recognition of these conditions will not be possible by palpation because the adenomata which have occurred in other glands are frequently quite small, as for instance in the pancreas. A patient with a pancreatic adenoma came to operation at the Brigham Hospital, and in this case the tumor was only 0.5 cm. in size. In order to make the diagnosis some method is needed by which one can inspect the gland, rather than only palpate it. For instance, a bilateral vertical incision just outside the recto-spinæ group of muscles in the back will allow you to see the adrenal gland quite well. This means two incisions, but I don't believe one will be able to make an adequate diagnosis in any other way.

SOME UNUSUAL CASES OF FILARIASIS OF THE SCROTUM AND GROIN

HUGH H. YOUNG, M.D.

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

Although filarial disease is relatively uncommon in the United States, we have had a number of cases of lymph-scrotum due apparently to the filaria sanguinis hominis. Filarial disease of the scrotum not associated with elephantiasis has in our experience been very rare, but we have recently seen five cases which presented so many novel and interesting features that they seemed worthy of presentation.

Case 1.—Remarkable inflammatory enlargement of glands of groin associated with intrascrotal masses of chronic inflammation, probably due to filaria or some other tropical disease.

J. F., male, aged nineteen years, Colombia, S. A., was admitted June 11, 1926, complaining of swelling of both testicles. Family and past history were negative. The patient denied all venereal diseases. He was kicked in the scrotum about five years ago and this caused a swelling in or around the right testicle, which has gradually grown worse. Later on, the scrotal contents on the left side became involved. It has become tender on palpation and painful on exercise. Recently the inguinal glands have become enlarged. There were no urinary symptoms. Sexual powers were normal.

Examination.—T. 99, P. 80, B.P. 150/70, W.B.C. 7,800, Hb. 90 per cent. The patient was a well nourished, well developed young man. Head, chest and abdomen were negative. Genitalia: penis negative, no urethral discharge. Scrotum enlarged on both sides. Right side: The conditions present are shown in a diagram. The vas was normal, the globus minor and body of epididymis were normal. The testicle was slightly enlarged, but normal in consistence. Covering the upper portion of the testicle and extending down over its surface to the lower pole was a peculiar, somewhat irregular enlargement. This was closely adherent to the testicle, and seemed to be attached to the globus major. Extending upward were two lines of induration, one of which contained one nodule and the other two nodules. These extended along the cord, but apparently were not attached, either to the vas or the veins. They were not adherent to the skin, but formed subcutaneous irregular lines of induration.

Left side: There was a larger hydrocele, the wall being thicker than on the right. There was no mass in the cord. The testicle seemed a little larger than normal. Epididymis: globus minor was in normal position, slightly enlarged, slightly indurated, distinctly adherent to testicle. The body was about normal in size, but slightly indurated. The outlines of the globus major could not be discerned. It was included in a mass which involved the testicle in its posterior portion. The mass was quite hard, somewhat irregular, about 1.5 x 2 cm. in size. The vas was normal. There were no masses, nodules or other lymphatic enlargements present, but the veins felt thicker and firmer than normal. Just below Poupart's ligament was a mass of glands extending from a point just external to the external ring upward for about 7.5 cm. and then outward and downward to the femoral space. In this region discrete and confluent hard glands could be felt. They were found in lines and also separately located. At least eight or ten large glands were present. No glands were felt along the inguinal canal, but by deep pressure in the inguinal fossa, glands could be made out. In the right groin a small mass of glands was present below Poupart's ligament. The inguinal canal was negative. Urine was clear, no shreds, microscopically negative. Rectal: Prostate was slightly broader than normal, median furrow and notch shallow. Tissues in midline were elastic below, indurated at upper end. Right lobe, drawn outward, was markedly indurated on outer edge, elastic near center. Left lobe was not enlarged, but indurated along outer edge, elastic towards center, slightly adherent. Right seminal vesicle was elastic, not adherent, not enlarged, not tender on pressure.

Comment.—The induration, both along the vesicles and right lobe of prostate, seemed to be periprostatic rather than intraprostatic. The conditions present were different from anything I have seen in tuberculosis. On deep pressure and massage, the adhesions were found to be very dense. The prostate, which seemed to be almost normal, was massaged to obtain secretion, that was microscopically normal.

Other glands: The epitrochlear glands were enlarged on both sides, as shown in the body chart (Fig. 1). On the right side they formed a mass about 1.5 cm. in diameter, and 3 cm. long, not tender. On the left side they were distinctly tender, much larger, about 2.5 cm. in diameter and 3 cm. long, somewhat irregular. The left axilla contained an irregular mass of more or less discrete glands, which were enlarged and hard. In the right axilla similar glands were found. Neck: In the posterior triangle, a few discrete, distinctly palpable, slightly enlarged glands were made out. Anterior triangle: enlarged glands in front of muscles and beneath angles of jaw were present, not tender. Posterior auricular glands were also palpable, apparently not tender, no glands palpable in the popliteal space. Muscles everywhere were firm. On the inner side of the triceps femoris muscle was a small mass about 3 cm. wide and 6 cm. long. It was apparently beneath the

fascia and did not suggest glands. It might be enlargement of muscles, possibly cystic. Just above the umbilicus was a small nodule about 1.5 cm. in diameter. Just to the right of the median line a similar small nodule was present midway between umbilicus and ensiform.

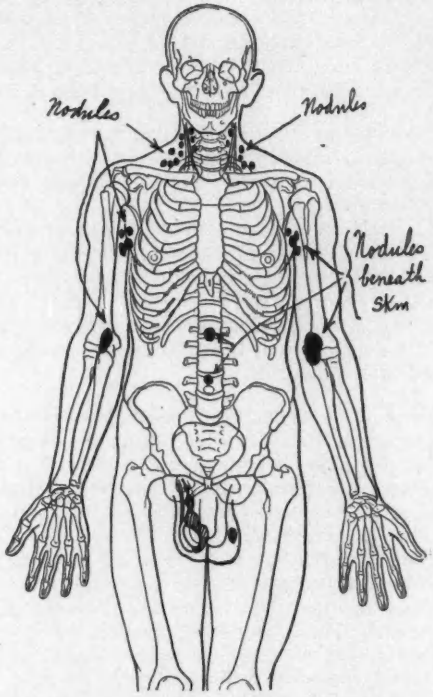

Fig. 1. Case 1. Chart showing condition on admission June 11, 1926. Enlarged glands in various parts of the body, and indurated areas of scrotum, not involving the vas, and only a portion of the epididymis.

Study of Blood for Filariasis (By Dr. deRivas Laboratory of Clinical Medicine and Pathology, Philadelphia): The blood was examined about every four hours, beginning May 26 at 2 P. M., and ending the next morning. Similar studies were made at 6 P. M., 10:30 P. M. and 2 A. M. Result: microscopic examination of blood during twenty-four-hour cycle did not show presence of microscopic filaria, either by

the common fresh cover-glass preparation or in the sediment of 1 c.c. of blood collected from the finger and treated by the acetic acid concentration method.

On June 14 blood examination showed Hb. 90 per cent, R.B.C. 4,200,000. Differential count was normal. Wassermann reaction was negative. Complement fixation for tuberculosis was negative. Differential count as to the matured and embryonic type of lymphocytes with reference to leukemia was negative. Blood chemistry was normal, sugar 97 mg. per 100 c.c., urea 10.9, and uric acid 2.0. The feces showed a few ova of trichocephalus. The urine was normal.

Impression.—Peculiar masses of inflammatory infiltration attached to testicle and globus major of epididymis with glands of groin in a young man from tropical South America. Filaria suspected. Operative removal was indicated.

On June 23, 1926, operation (Young) was performed using gas, oxygen and ether: *Excision of chain of chronic suppurative masses within scrotum, and attached to testicle, epididymis, and tissues of cord.* Vas deferens was apparently normal. Epididymis was involved only in globus major. Testicles were not involved. Veins of testicle and cord were partly injured, but mostly preserved. Vas was uninjured. Incision was closed.

Detailed Comment.—An incision about 3 inches long was made in the anterior surface of the scrotum. Before reaching the dartos, and between it and the skin, several small, yellowish gray bodies surrounded by closely adherent fibrous tissue, were discovered (Fig. 2, No. 1). These were dissected free and kept for specimens. The dartos was then opened. The tunica vaginalis was found obliterated and very adherent to the testicle. There was no distinct sac around the testicle and no hydrocele, but the tissues around the testicle and cord were very fibrous and markedly adherent, thus making it difficult to differentiate the structures around the testicle, but it was finally demonstrated definitely that the vas was not involved. The globus minor and body of epididymis were adherent to the testicle, but apparently not enlarged or indurated. Closely adherent to the anterior surface of the testicle was an elongated mass of induration which started near the lower end (Fig. 2, No. 2) and traveled along the anterior surface, becoming larger until finally it joined another rounded mass 2 cm. in diameter, which was closely adherent to the upper surface of the testicle. In dissecting this free, a pus cavity was opened. The pus which escaped looked tuberculous in type. This mass was so adherent to the globus major of the epididymis that it seemed wise to cut into the top of the globus major, a portion of which was removed with the mass. The testicle was not cut into or injured. All the inflammatory tissues were apparently removed, taking a few veins, but leaving a sufficient number to supply the testicle and remaining epididymis.

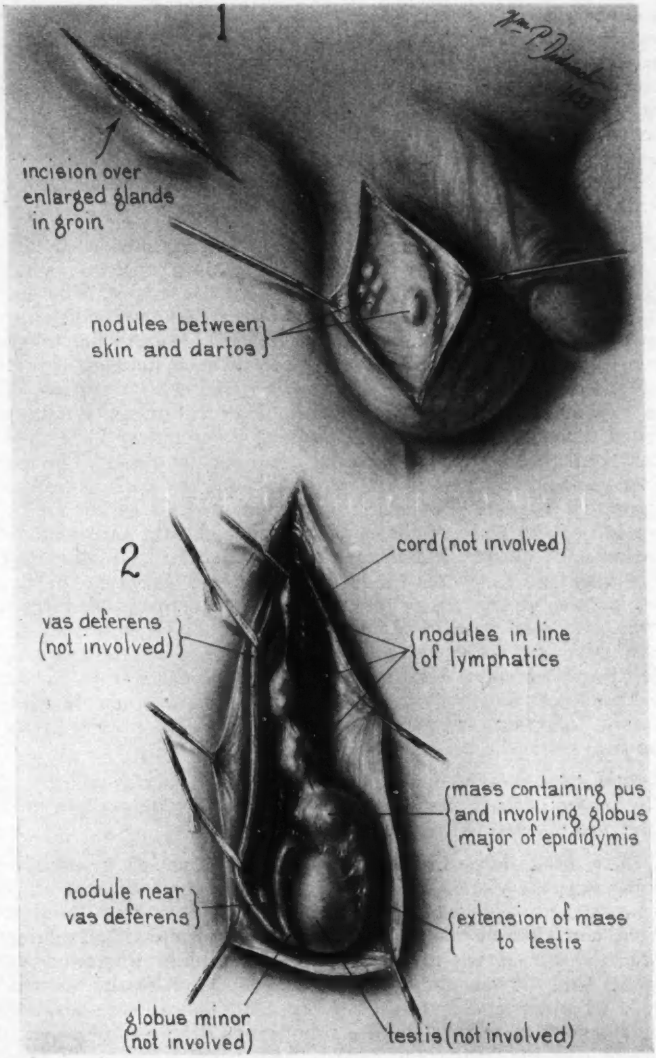
1
incision over enlarged glands in groin
nodules between skin and dartos
2
cord (not involved)
vas deferens (not involved)
nodules in line of lymphatics
mass containing pus and involving globus major of epididymis
nodule near vas deferens
extension of mass to testis
globus minor (not involved)
testis (not involved)

Fig. 2. Case 1. From sketches made at operation: (1) showing nodules beneath skin; (2) the condition after opening dartos and tunica vaginalis.

In the extreme upper end of the scrotum a long body 5 mm. in diameter and 10 mm. long was found. This was connected by a line of fibrous tissue with a little larger mass about 8 mm. in diameter, and below this was a still larger globular mass about 1 cm. in diameter, this being immediately above the mass 2 cm. in diameter in the upper portion of the testicle. Hemorrhage was well controlled. The wound was closed in layers by sutures.

A separate incision was made in the groin, and a small mass of fat with a few lymphatic glands was removed for study.

Pathology.—The specimen consisted of a mass measuring about 8 cm. long and from 2 to 5 cm. wide. There was a separate mass, probably containing glandular tissue, about 2 x 3 cm. in size. The epididymis was surrounded by a large mass of scar tissue, of which sections showed marked chronic inflammatory reaction around the tubules of the epididymis, and considerable chronic fibrous inflammatory tissue surrounding the epididymis. There was round cell infiltration. There was nothing suggesting tuberculosis. The section of lymph gland showed chronic inflammation and nothing tuberculous. Other sections taken from the larger mass showed a similar condition. The diagnosis was non-tuberculous epididymitis with marked peri-epididymal inflammatory reaction. The larger mass contained the globus major and a portion of the body of the epididymis, which was surrounded by a large mass of chronic inflammatory tissue that had also involved the tunica vaginalis (see description of operation). Sections showed tubules of the globus major of the epididymis surrounded by thick fibrous tissue and marked round cell infiltration. Outside the body of the epididymis there was a great deal of chronic inflammatory tissue, which in places showed areas of necrosis. Sections from the lymph gland removed showed evidence of chronic inflammatory reaction, but nowhere was there any evidence of tuberculosis present, nor any areas suggesting the presence of filaria.

Convalescence.—The wounds healed well, except for a small sinus at the upper part of the incision, which was draining slightly. The patient was discharged on July 12.

Second Admission.—On October 2, 1926, the patient returned complaining that the glands in the left groin had enlarged, and an indurated mass had appeared in the left side of the scrotum. This had increased considerably since his first visit to hospital. Examination showed the left testicle normal. The globus minor was only slightly irregular, and the vas was not enlarged, but the globus major was enlarged, irregular and indurated (Fig. 3). There were no nodules along the cord as in the opposite side before the first operation. On the right side the fistula had closed. There was a moderate cicatrix, the testicle seemed to have atrophied somewhat and was quite hard. The cord was normal in size, slightly indurated. There was no re-

currence of the pathologic process. Several enlarged glands were present in the left groin. Condition of prostate and vesicles was the same as before, with periprostatic and perivesicular infiltration and adhesions. Prostatic secretion consisted of mucus and occasional pus cells, no spermatozoa, no red cells. General health was excellent. Urine was normal.

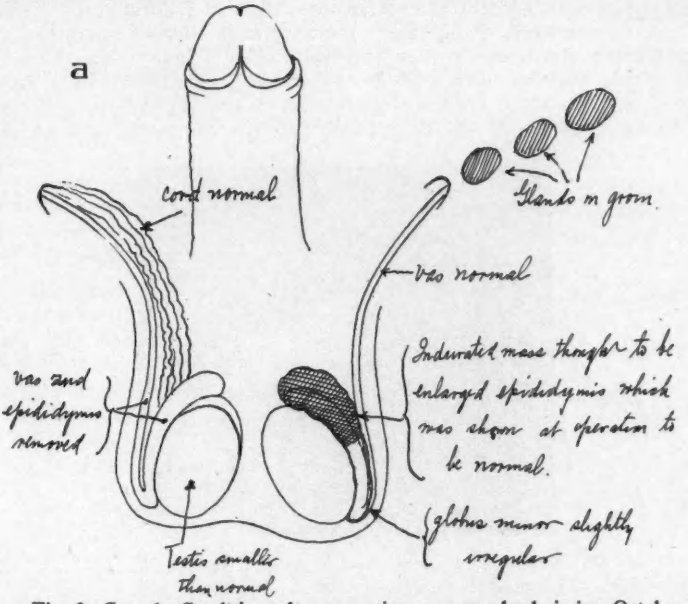
a
Cord normal
Glands in groin
Vas normal
Indurated mass thought to be enlarged epididymis which was shown at operation to be normal.
Vas and epididymis removed
Testis smaller than normal
Globus minor slightly irregular

Fig. 3. Case 1. Condition after operation on second admission October 2, 1926. Right side negative; left side shows marked increase in mass within scrotum and glands of groin.

On October 4, 1926, operation (Young) was performed using gas and ether: *Excision of suppurative and inflammatory area between testicle and epididymis posteriorly on left side.*

Epididymis, vas and testicle were not injured. Glands of groin on left side were removed through the same incision, which was a high scrotal and inguinal incision. Stab drainage was used with protective wick for drainage.

Detailed Comment: The incision was made over the glands in the groin and upper portion of scrotum to remove both at one time. The scrotal contents were delivered through the wound and examination showed the vas deferens normal. It could be followed down to the

epididymis, where inspection showed that the tunica vaginalis was extremely hard and thick. It was opened on the anterior aspect and found to be 5 mm. thick and densely adherent to the testicle, there being no space between the two. The operation was carried out with difficulty. The epididymis was apparently normal throughout, but on the posterior aspect of the testicle and apparently between the testicle and epididymis, which was external to it, was an indurated mass about 2 cm. in diameter. Note that on examination, before operation, the epididymis was described as involved. The veins of the cord ran along the superior and inferior aspect of this inflammatory mass, which was dissected from the epididymis, veins and testicle with some difficulty, rupture finally occurring, with the escape of creamy pus.

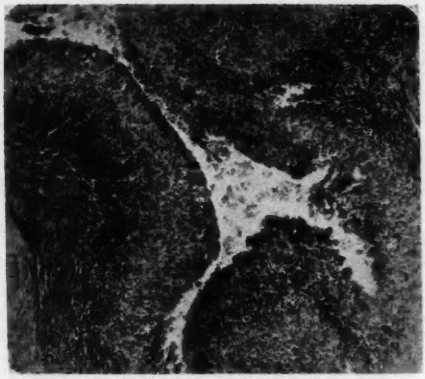

Fig. 4. Case 1. Section showing the lymph channels containing necrotic material and white cells, the lumen lined with endothelium. Marked infiltration of lymphocytes in the wall.

The wound was treated with 1 per cent mercurochrome. The testicle, epididymis and veins, which were apparently not indurated, were replaced in the scrotum, and the glands of the groin were then excised. These formed a chain of confluent and discrete glands varying from 1 to 1.5 cm. in size. They were largely superficial inguinal glands, but two, which were in the femoral region, were also removed. They were considerably enlarged and moderately indurated. The patient stood the operation well.

Pathology.—The specimen consisted of three pieces, the largest mass measuring 6 x 2 x 2 cm., and was composed of several 1 cm. lymph glands imbedded in fat and fibrous tissue. The glands were firm. One portion, measuring 3 x 1 x 0.5 cm., represented thickened

peri-epididymal tissue, on one surface of which the tunica vaginalis appeared normal. The smallest specimen measured 1 x 1.5 x 0.5 cm., was soft, rubbery and contained numerous small necrotic nodules.

Microscopic examination showed increased lymphoid tissue in the inguinal glands. A section from the tunics showed thickening of the vaginalis and cremasteric fascia and chronic inflammatory reaction around the vessels of the cord. The peri-epididymal structure showed on section numerous tubular structures filled with necrotic substance. The walls of these tubules were composed of fibrous tissue surrounded by a zone of lymphocytes (Fig. 4). These tubules did not resemble epididymis—no lining membrane was seen. They might represent dilated lymphatics. There was round-cell infiltration around the vessels leading to the testis.

Impression.—Chronic inflammatory process, non-tuberculous, involving the tissues over the globus major of the epididymis, testicular tunics and spermatic cord. Inguinal adenitis. Careful search for micro-filaria was negative.

Bacteriologic Note.—Careful smears from tissue removed at operation, and the pus, were entirely negative for bacteria and filaria. Cultures were taken and guinea pigs and rabbits inoculated. All subsequently were reported negative.

The patient had an uneventful convalescence. The wounds healed per primam, and the patient was discharged on October 14, 1926, in excellent condition.

On November 9, 1927, the patient returned for observation. He stated he had been well, had no pain, fever or other symptoms. The scrotum was considerably enlarged by a hydrocele on the left side. The lower portion of the testicle was palpable. The epididymis was slightly thickened and flattened against it. The upper portion was concealed by the hydrocele sac. There were no nodules, no tenderness, no adhesions or fistula. The vas and veins were negative. Incisions in groin were well healed, with moderate cicatrix, and no palpable glands. The right side of scrotum was much smaller. Testis was markedly atrophic. The epididymis was nodular, moderately indurated, not adherent. There was no fistula, no tenderness, no abscess. The vas and veins were negative.

Letters received from the patient stated that he was enjoying the best of health (August 23, 1928) and that he had remained entirely well (December 3, 1931).

A letter from Dr. D. deRivas dated December 11, 1931, gives the following information: "As to the histopathologic examination of the tissues removed, a portion of which I took with me, I came to the conclusion that this was a case of chronic granuloma, with degeneration and some necrotic areas very suspicious of atypical form of chronic tuberculosis. I was, however, unable to find any typical tubercles or giant cells in the lesions. I likewise inoculated the material into guinea pigs with negative results. As to the possibility of filaria-

sis in this case, I did not find any evidence of that condition, as the section did not show the characteristic lymphangitic lesions, commonly seen in elephantiasis, nor microfilaria in the section. I examined him two years ago and found no evidence of elephantiasis in any part of the body. The operation has been successful, and there is no evidence of any recurrence."

Comment.—The lesions, which Dr. deRivas thought should have been present, may exclude filaria sanguinis hominis, but not onchocercus volvulus, as will be shown later on.

Case 2.—Man of twenty-two years with indurated cord in scrotum on both sides and enlarged glands of groin, probably due to filaria. Operations. Recurrences.

C. A. P., male, aged twenty-two years, of Colombia, S. A., was admitted September 12, 1928, complaining of fistula in the right side of the scrotum. Family history was negative. Three brothers and two sisters are living and well. Past history was of the usual childhood diseases. The patient has always been well and healthy until one year and a half ago. There was no venereal history. Sexual powers were normal. One and one-half years ago the patient injured himself while riding on a rough road in an automobile, by striking his scrotum against the seat of the car. Both testicles became moderately swollen after this, and on the left side the swelling softened, broke down and a fistula formed about four months after the accident. This fistula finally healed, and he has had no further trouble on that side. Seven months ago the right testicle became swollen and, a month later, a fistula developed on that side, with discharge of pus which had an odor. This fistula has never healed. The patient lived in Cartagena, Colombia, South America. His general health was excellent and there were no pains.

Examination.—T. 99, P. 80, R. 20, B.P. 128/80. The patient was a well developed, well nourished young white man with mucous membranes of good color, and no general glandular enlargement. Head, neck, thorax and abdomen were negative. Genitalia: penis negative. The right side of the scrotum was swollen and there was a small fistulous tract on the anterior surface about midway between the bottom of the scrotum and the groin. This sinus led to an indurated cord, which extended downward for a distance of 4 or 5 cm., and involved the upper part of the epididymis, as shown in the accompanying diagram (Fig. 5). This mass was about 2.5 cm. in diameter. The surface was indurated, not adherent to the skin, except at the sinus. The vas was apparently not involved, although the mass was adherent to the vas at a point about 2 inches above the testicle. Above and below that point the vas was negative. Veins were not involved; testis apparently normal. The scrotal induration did not extend above the sinus, the cord above that point being normal. The glands of the groin were considerably involved. The left testis, epididymis and vas were negative.

There were four indurated, moderately enlarged glands in the right groin. None was made out in the left. Rectal: prostate more prominent than normal, both lobes slightly indurated and adherent. Vesicles also were slightly indurated and adherent; between testicles tissues were negative.

Urine: acid, 1.020, albumin and sugar 0; microscopic negative. P.S.P.: app. 4 mins., half-hour readings, 50, 25, 5 and 5 per cent:

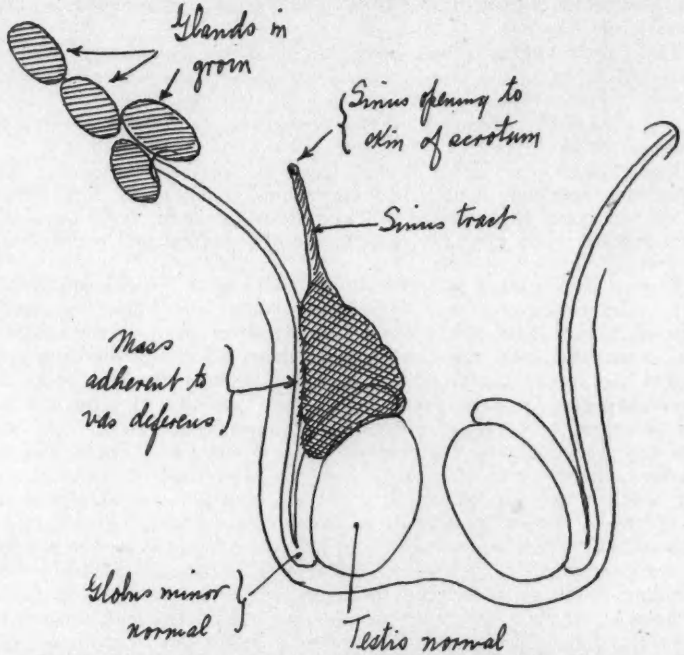

Fig. 5. Case 2. Chart on admission September 12, 1928. The vas and lower half of epididymis are not involved. The sinus leading to the subcutaneous indurated mass is seen. Most of it is outside the spermatic cord. Glands of groin are shown.

two-hour total, 85 per cent. B.U. 48, B.P. 118/75. Laboratory: direct smears from urine—no acid-fast bacilli found. Guinea pig inoculated. (Late report: negative.) Culture: sterile. Studies from scrotal sinus were negative for tuberculosis. R.B.C. 5,160,000, W.B.C. 7,800, Hb. 90 per cent. Studies of blood for filaria at midnight were negative.

Impression.—"I think this is a case of chronic inflammatory in-

volvement of the glands of the groin, and of the scrotal tissues along the cord, involving the epididymis on the left side, the etiology of which is not clear. I would advise x-ray of lungs to eliminate tuberculosis, excision of glands of groin, and indurated areas in scrotum. One must think of filaria." (Young.)

On September 14: operation was performed (Young) using gas, oxygen and ether anesthesia: *(1) Resection of inflammatory mass in scrotum which involved the right epididymis (epididymectomy and partial vasectomy.)*

The tunica vaginalis was opened and almost completely resected. The testicle was not injured; dartos was closed over testes with plain catgut. The skin was closed with clips.

(2) Excision of glands in right groin, including some of those along femoral canal.

The glands were not followed beneath Poupart's ligament. The saphenous vein was ligated and the wound closed with clips. Anesthesia was good, hemorrhage well controlled, and the condition of the patient good. The operation was apparently radical and satisfactory.

Remarks.—Through the scrotal incision (Fig. 6, No. 1) the testicle was brought out, the tunica vaginalis opened and inspection made. This showed a mass which slightly involved the head of the epididymis. From there this mass, which was about 1.5 cm. in diameter, extended backward, involving the tunica vaginalis. From this point the mass extended upward externally to the cord and in front of the vas deferens, to which it seemed to be loosely adherent. The vas deferens was not actually involved (Fig. 6, No. 3). There was no fusiform involvement of the vas such as I described in my examination, but an extracordal nodule. From the upper end of this mass an indefinite line of induration extended upward and forward to an area of induration in the skin, which had probably been the site of a previous sinus. This was excised with a portion of the skin surrounding it. Epididymectomy and vasectomy were carried out for a distance of 10 cm.; the upper end of vas was injected with 5 per cent argyrol and ligated. It was impossible to detect any continuous line of lymphatics from the scrotum to the glands of the groin, which were removed through an oblique incision in the groin (Fig. 6, No. 2).

Pathology.—The specimen consisted of two pieces, the larger made up of vas, epididymis, tunica vaginalis and an indurated tract connected with a portion of the skin of the scrotum. It measured 14 x 9 x 1.5 cm., and weighed 32 grams. The epididymis was firm and nodular on palpation. The globus major was grayish-white in color and on section cut with some resistance. The cut surface was also grayish-white. There were three caseous areas which measured 2 mm. in diameter. The body of the globus minor was firm, but no nodules were felt. The tunica of the testis was thickened and rubbery in con-

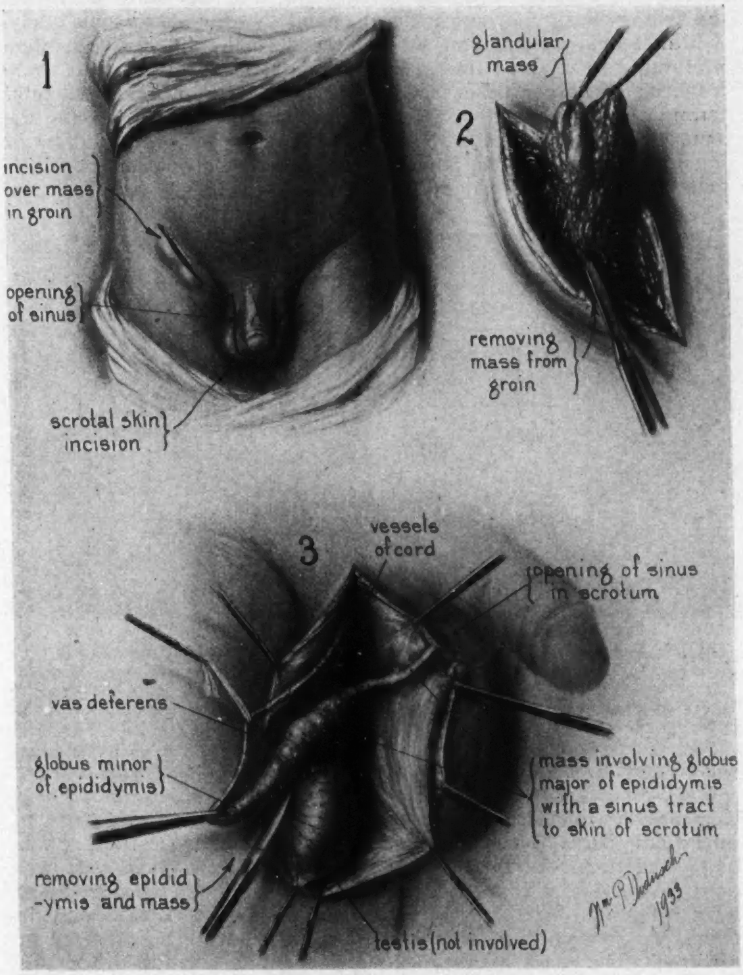

Fig. 6. Case 2. The operation: Excision of sinus tract and inflammatory mass external to cord, but involving epididymis; also excision of glands of groin.

sistence. There was a firm band of tissue running out to a piece of skin, which was removed from the scrotum. Sections were taken from the skin, globus minor and body of epididymis for microscopic study.

Microscopic examination showed the normal skin of the scrotum perforated by a sinus tract. The walls of this drainage tract were made up of fibrous tissue surrounded by a zone of round-cell infiltration. The inflammatory reaction extended for 0.5 cm. around the sinus, which led to a necrotic area posterior to the globus major of the epididymis. Sections from the globus major showed the epididymal tubules greatly dilated. The lumina were filled with testicular

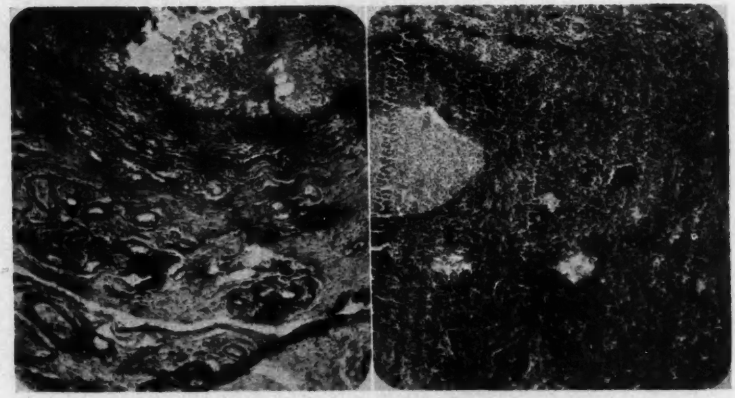

Fig. 7. Case 2 (*left*). Transverse section of portion of spermatic cord with adherent, indurated mass, the central portion of which contains necrotic material surrounded by round-cell infiltration which is separated from the cord by layers of fibrous tissue. This shows that the lesion is external to the fascia covering the cord, as noted in other cases.

Fig. 8. Case 2 (*right*). Section of lymph gland from the groin, showing chronic adenitis and the central cavity filled with necrotic material.

elements showing immature spermatozoa. There was a decrease in interstitial tissue. The high columnal epithelium of the tubules was quite well preserved in some instances, but for the most part was flattened out by internal pressure. The globus major was surrounded by a dense, fibrous tissue with large necrotic areas 2 to 3 mm. in diameter. Sections through the spermatic cord were not invaded or involved. The mass at various places showed necrotic areas surrounded by fibrous tissue and a zone of lymphocytes (Fig. 7). No tubercules, giant cells or polymorphonuclear cells were seen in the section. The hydrocele sac showed a thickened tunica vaginalis and large bundles of cremasteric muscle. There was great increase in

fibrous tissue without round cells. The vessels appeared normal. Sections from the inguinal glands showed evidence of reaction to a chronic inflammatory process (Fig. 8). There were no microfilaria or adult worms.

Impression.—Chronic inflammatory disease, non-tuberculous, involving the tissues surrounding the epididymis. Scrotal sinus-tract showing chronic inflammatory reaction. Epididymitis, chronic secondary. Inguinal adenitis. A careful search for parasitic worms, or their remains, failed to demonstrate filaria.

Convalescence.—Wounds healed per primam. The patient was discharged October 1, 1928, in excellent condition.

Second Admission.—On October 26, 1928, the patient returned with swollen glands in the left groin. These glands formed a chain about 1.5 cm. in diameter and 5 cm. long, all above Poupart's ligament. Perhaps one of the glands was in the femoral canal. Two glands were palpable along the saphenous vein. The skin was everywhere freely movable, no areas of fluctuation, no tenderness. The upper part of the scrotum was negative. Testis, epididymis, vas, veins and peritesticular tissues were negative. No induration was made out in the left side of the scrotum. The wound in the right side of the scrotum was now well healed. There was very little cicatrix. The wound in the groin was well healed; moderate cicatrix; no glands.

Comment.—Excision was indicated.

On October 25 the patient was admitted to hospital; W.B.C. 9,400, Hb. 85 per cent, B.U. 40, B.P. 113/80, P.S.P. 90 per cent in two hours.

On October 26 operation was performed (Davis) using ethylene. *Excision of glands of left groin.* An incision was made along Poupart's ligament, curving downward at the inner end to expose the femoral triangle. Five or six enlarged glands forming a chain were removed by blunt dissection. The lowest extended well down into the femoral triangle. No suppuration was encountered. Closure was made with No. 1 plain catgut for subcutaneous tissue, silk for skin. A very small rubber tissue drain was used at lower angle of wound, to be removed in twenty-four hours.

Pathology.—Glands were palpable in the masses of fat. One section taken from one of the lymph glands showed numerous round cells, with germinal centers. A large part of the gland had been destroyed by dense round-cell infiltration. Very few trabeculæ were seen. There were no giant cells or tubercles. Diagnosis: adenitis, chronic, non-tuberculous. No filarial organisms or debris found.

Bacteriologic Note.—Study of glands removed at operation: direct smear—acid-fast Gram and Wright stains used. No organisms or

Donovan bodies were seen. Cultures (three days) showed scant growth of staphylococcus; held for identification. It was planned to hold cultures for two weeks for possible growth of other organisms. Two guinea pigs were inoculated for possible tuberculosis. One rabbit was inoculated intratesticularly for possible syphilis. No evidence of filariasis or infection with hemophilus ducreyii (J. H. Hill).

Postoperative Course.—The patient was discharged November 17 in good condition, a portion of the wound healing by granulation. Careful examination before discharge showed no general glandular enlargement. Urine was clear, 1.016, microscopically negative.

A letter from Dr. Calvo, Cartagena, Colombia, S. A., dated January 1, 1929, reads as follows:

"For several days the patient has suffered from what seems to me a new focus in the scrotum. I see from your letter that it was not possible to determine the etiology. In my opinion, filaria may be the cause of such a case, even when it has not been possible to discover the larva by the microscope. There are many reasons, especially clinical, to suspect it. The family of this youth has carried filaria for two generations, to my knowledge. There are members who now have manifestations of this disease, and of a clinical type (exanthema of an extensive area of the skin, with a line of indurated glands leading to it, vomiting, chills and fever, reaching 40 to 41 centigrade, intensive headache and pain in the affected member). These crises are reached at intervals of days, months or, on occasions, years. These correspond to acute attacks of lymphangitis, which is the form most common of the superficial or cutaneous manifestations of the disease, but in other cases it assumes forms which simulate hepatic, renal or even appendiceal colics and crises, when the syndrome has for its anatomic seat the deeper lymphatics of the abdomen. I think, in this case, it is possible to make a clinical diagnosis of filariasis. The difficulty of finding the larva of filaria of Bancroft in the blood is, I know, very great."

On September 14, 1931, a letter from the father, who is a physician, stated:

"My son feels generally well, but very frequently small localized swellings have appeared in the scrotum, which disappear after five or six injections of neosalvarsan. He is also taking tincture of iodine in doses of 20 drops. This upsets his stomach. Before the swelling appears in the scrotum the patient feels pain in his abdomen near the groins. He feels nothing else."

Case 3.—Filarial disease of both sides of scrotum. Left most extensive; removed by castration.

A. J. del., of Cartagena, Colombia, male, aged forty-nine years, was admitted to the hospital December 12, 1928. At the age of twenty-four the patient had a penile chancre which was cauterized. The Wassermann reaction was negative. In 1919 he had left renal colic, but there was no hematuria, and no stone was passed. He suffered a long time from headaches. On examination, albumin was found in the urine. Blood pressure was said to be 220, and a diagnosis of nephritis was recently made. Since childhood the patient has had

pains in both legs. Twenty years ago the left testicle became swollen and this has persisted until the present time. Intercourse satisfactory.

Examination (Dr. Andrus).—The eyes were normal, except that the arteries were slightly narrowed and tortuous. The teeth were in good condition, and the glands at the angle of the jaw were hardly palpable. The heart was slightly enlarged. The abdomen was nega-

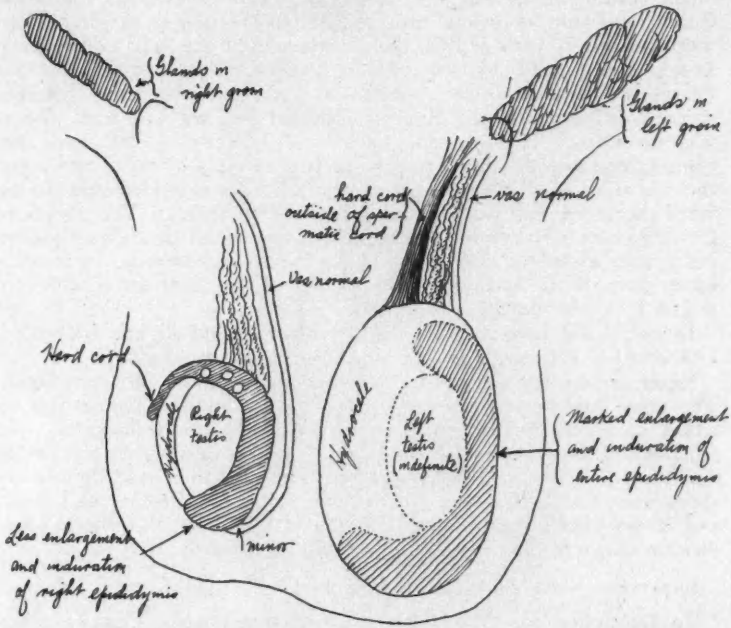

Fig. 9. Case 3. Chart on admission December 12, 1928. Although both epididymes are involved, there was no involvement of the vas, and on the left side there was a hard cord outside the spermatic cord, which led to much enlarged glands in the left groin.

tive. The blood pressure was 190/120. The extremities were negative. There was no edema.

Impression.—Hypertension, slight cardiac enlargement, and nephritis(?).

Genitalia: The penis was negative. The right testicle was surrounded by a small hydrocele with a thin wall (Fig. 9). The epididymis lay to the inner side. The globus major was slightly larger

than normal, somewhat irregular, soft in places and indurated, and in others cystic. The body was enlarged and indurated. The globus minor was considerably enlarged, and the induration was of second degree. It was not adherent to the skin. There was no sinus, and no tenderness. The right vas was normal in size, connected with the epididymis normally and could be palpated to the external ring. Running downward and outward from the globus major was a peculiar small cord lying outside the tunica vaginalis. This cord was about 2 cm. long and lay below and external to the globus major. There were no other cords within the scrotum. On the left side a fairly large, thin walled hydrocele was present. The testicle was not definitely palpable. The epididymis was considerably enlarged throughout, was smooth, slightly indurated and not adherent. There was no sinus. The vas was negative. Anterior to the veins and running down to the upper part of the hydrocele sac was a cord about the size of a small lead pencil (5 mm.). This extended upward toward the groin, and was lost in the fat of the pubes. The glands of the left groin were slightly enlarged and indurated throughout, forming a mass about the size of the finger. This extended down into the upper part of the scrotum. The glands of the right groin were enlarged to a less extent.

Rectal: The prostate was slightly enlarged and slightly indurated. The vesicles were negative. There were no enlarged glands.

Extensive studies showed the blood chemistry to be entirely normal. The urine had been consistently free from albumin even during an attack of acute tonsillitis while the patient was in the hospital. No red blood cells were seen at any time. Specific gravity in concentration test varied from 1.000 to 1.030. The phthalein test showed an appearance time of 5 mins., 40 per cent eliminated the first half hour, and 72 per cent in two hours. The blood urea was 28. Blood pressure on entrance was 140/120, later 178, and finally 160.

Impression.—An operation is indicated.

On December 26, 1928, operation was performed (Young) using ethylene: *Left orchidectomy.*

A high scrotal incision was made and small, indurated cords with little white nodules two to three times the size of the cords were found running in the tissue adjacent to the spermatic cord upward toward the groin. They were opalescent in appearance and seemed to be imbedded in the tunics and upper portion of the epididymis and testis. The testis seemed to be of normal size, but was surrounded by a hydrocele also slightly opalescent in appearance. Fearing the infection might be spread by partial operation, and not being able definitely to determine the nature of it, it was decided (Young) to carry out an orchidectomy. Accordingly the testis and tunica were freed by blunt dissection from the lower part of the scrotum, and delivered into

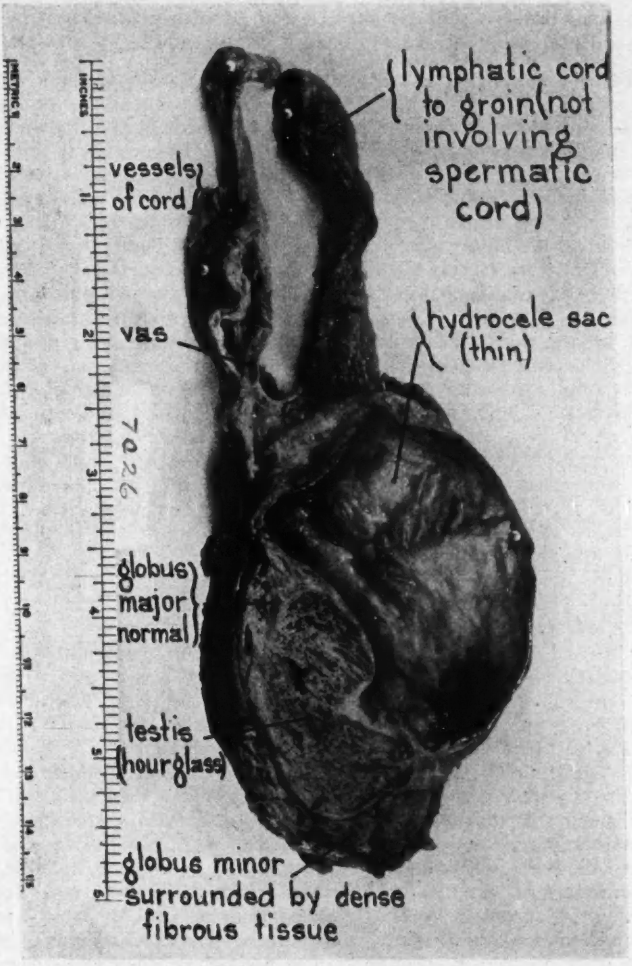

Fig. 10. Case 3. Photograph of specimen removed at operation. The mass in epididymis is shown in section. Note that the indurated cord leading to groin is outside the spermatic cord.

the wound. The cord was then freed as far as possible above the opalescent body, and ligated high up, apparently with a good margin of normal tissue. The dartos was sutured with plain catgut, and the skin with interrupted sutures of black silk (James).

Pathology.—The specimen measured 18 x 8 x 5 cm., and weighed 170 grams. It consisted of testis, epididymis, cord, vas and structures in cremasteric fascia removed in one piece. The hydrocele sac contained about 100 c.c. straw colored fluid. The wall was thin (Fig. 10), measuring from 1 to 2 mm. in thickness. The testis was about normal in size and consistence and measured 4 x 3 x 3.5 cm. The midportion was constricted by a band of fibrous tissue which gave it an hour-glass appearance. The globus major and minor of the epididymis were closely applied to the posterior surface of the testis and were encased in a thick, fibrous sheath from top to bottom. This sheath was from 2 to 5 mm. in thickness and about 2 cm. in width. This broad, thick, fibrous mass which completely covered and obscured the entire epididymis, was on preliminary examination thought to be simply enlarged epididymis. No nodules were palpable in the epididymis. The vas deferens was normal in size and consistence, as were the veins of the spermatic cord. External to these veins was another cord about 6 cm. long and 7 mm. in diameter, which contained fine yellow strings with small nodules 2 to 4 mm. in diameter in the form of a chain. Several of such beaded chains were visible. Sections were taken from these, from the globus major and minor of the epididymis and from the testis.

Microscopic sections from the testis showed normal testicular tubules. The tunica albuginea was considerably thickened and diffusely infiltrated with round cells. The vessels supplying the testis were normal. The tubules of the globus minor of the epididymis were dilated. Their walls were thickened and there was a very great increase in fibrous tissue surrounding the globus minor. There was no evidence of active inflamamtory disease, except immediately around the smaller blood vessels where the reaction was chronic. The blood vessels were much larger than normal. A section through the vas deferens showed it to be perfectly normal. The vessels of the cord were larger than normal, but presented no inflammatory change. Sections from the globus major showed flattening of the tubules. There was an increase in fibrous tissue around the epididymis. There was great increase in vascularity. Sections from the nodular cord accompanying the spermatic vessels showed a great deal of loose areolar tissue, fat and fibrous tissue. The vessels were extraordinarily large. There were no areas of necrosis. The nodules in this cord had apparently been produced by a grouping of the vessels in such a way that they interlaced, and we found areas of increased fibrosis at these points. At the edge of one of these sections, in a position corresponding to the fine white cord, as seen at operation, there was a tubular

structure made up of fibrous tissue, dividing up into five sectors. The lining of this tube was endothelium, and had the appearance of a dilated lymph vessel.

Impression.—Fibrosis of the tunics of the testis and epididymis with great increase in vascularity. No active inflammatory process was observed, except around the vessels at the globus minor. There was an increase in the arterial supply as well as venous without varicosity. There was no evidence of tuberculosis and no microfilaria were seen.

The convalescence was uneventful. The wound healed per primam.

The patient was discharged on January 10, 1929, in excellent condition.

On January 15, 1931, the patient returned for observation. He was operated on in 1928. Since then he had felt perfectly well. He voided urine at normal intervals without pain or difficulty. His only complaint at this time was that erections were not as good as formerly. The prostate was not enlarged, tender or indurated. The secretion obtained by massage was perfectly normal. The urine was clear in three glasses and was negative. There was no evidence of recurrence or development of similar conditions elsewhere (Dr. Smith).

Case 4.—The following case of double epididymitis following prostatitis and seminal vesiculitis of the usual type in a patient who also came from Colombia, South America, is cited to show the marked differences of involvement within the scrotum between common infections and those produced by filaria.

J. H. E., of Barranquilla, Colombia, male, aged thirty-six years, was admitted March 3, 1930, complaining of two attacks of gonorrhea eighteen and fifteen years ago. Five years ago the patient had a severe cystitis and later hematuria, which was treated by cystoscopic fulguration. He is said to have passed some stones. He developed a severe right epididymitis, following a fulguration, and one year later had bilateral epididymitis. The induration in the epididymes had persisted. There had been a loss of sexual powers in recent years. There was no history of lesions in other parts of the body, or of enlarged glands.

Examination.—Hb. 60 per cent, W.B.C. 8,600, B.P. 110/70. The Wassermann reaction was negative. General examination was negative. The nodes at angle of jaw were hardly palpable. The inguinal glands were palpable, but there was no general glandular enlargement. The chest and abdomen were negative. Genitalia: The penis was negative, no urethral discharge. Scrotum was enlarged on both sides. The right testicle was about normal in size and consistence. There was no hydrocele present. The entire epididymis was considerably enlarged and moderately indurated, as shown in the chart (Fig. 11). It measured about 2 cm. in diameter, was fairly smooth, slightly tender, not adherent to the skin, and there was no sinus present. The

veins were very slightly enlarged. The vas deferens was not enlarged. There were no indurated cords or glands or nodules within the right scrotum. The groin was negative. The left testicle was about normal in size and surrounded by a small hydrocele. There was marked enlargement of the globus minor, which was about 2 cm. in

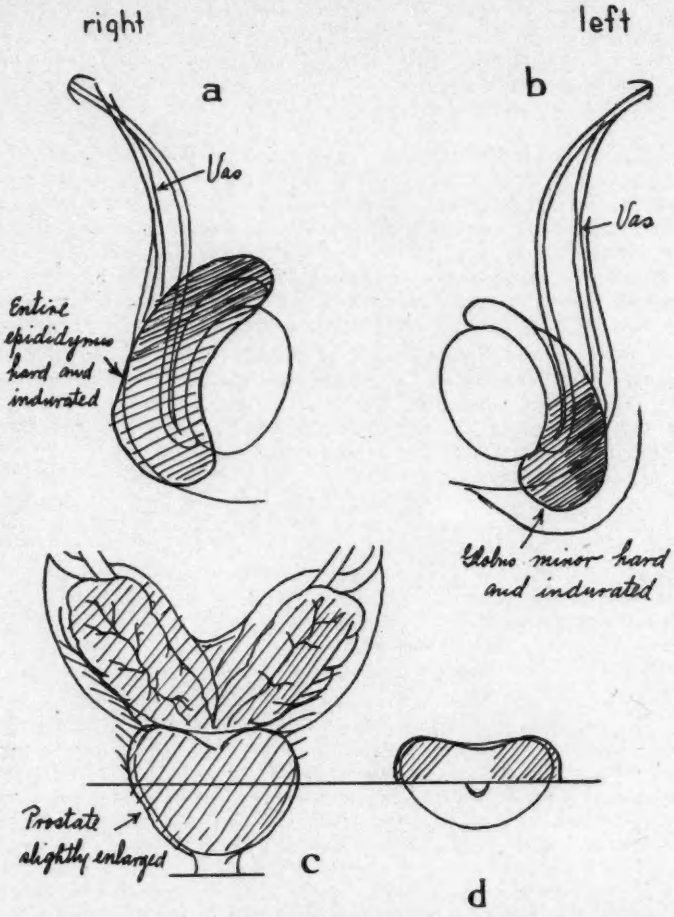

Fig. 11. Case 4. Charts on admission March 3, 1920. Both epididymes are involved, but there is no indurated cord external to spermatic cord. No glands of groin. Prostate and vesicles are slightly indurated.

diameter, and markedly indurated, as shown in the chart (Fig. 9). It was smooth, tender, not adherent to the skin, and there was no sinus. The vas was a little larger than normal and slightly indurated. The globus major was negative. The veins were only slightly varicosed, and there was no indurated cord within the scrotum. Rectal: The prostate was a little broader than normal, and median furrow and notch were wide and deep. The right lobe was slightly irregular, slightly indurated and adherent. The left was the same. Both seminal vesicles were slightly indurated, forming a plateau above the prostate (Fig. 11).

Examination of the blood at night for filaria was negative.

Impression.—Chronic prostatitis and vesiculitis; double epididymitis, non-tuberculous.

On March 10 the patient had been treated by prostatic massage and urethral injections without much benefit. The epididymes were still enlarged and tender. Epididymectomy was, therefore, advised.

On March 12 operation was performed (Young) using ethylene gas anesthesia: *Bilateral epididymectomy, partial vasectomy and injection of vasa deferentia with 10 per cent collargol on each side.*

The testicles and veins of cord were not injured. A small rubber drainage tube was inserted on each side. The skin was approximated with fine silk sutures. The condition at the end of operation was good. On the left side a lobulated hydrocele with numerous adhesions between the tunica vaginalis and testicle was found. The testicle was apparently not diseased. The epididymis was enlarged and indurated. The globus major was normal. The lower part of the body and minor were enlarged and quite hard. No indurated cord either within or outside the spermatic cord was found. On the right side the entire epididymis was enlarged and indurated.

Pathology—Résumé.—We have here a case of chronic epididymitis involving the globus minor of both epididymes, the globus major on the right side, and, to a very slight degree, the globus major on the left side. The infection seen in this case quite resembled that which we are accustomed to see in chronic epididymitis following acute pyogenic epididymitis. There is no tubercle formation in these sections. No giant cells were seen. This case had none of the characteristics of tuberculosis or syphilis. A careful search for filaria has been made. None of the actual parasites has been found, nor cross sections of one. There was apparently none of the lymphatic involvement which is usually seen in filariasis. I should rather put this case in the class of chronic epididymitis, non-specific.

The convalescence was smooth and the patient was discharged in good condition on April 1. Guinea pigs inoculated with tissues from the epididymis did not develop tuberculosis, and those inoculated from the urine also failed to show any tuberculous infection. Sounds were

passed with benefit in April. On May 12 the urine contained a few shreds, but no infection. Cystoscopy was negative. There was no residual urine. General condition was fine. No further report was obtained.

Since making the original report, a case almost identical with those presented has appeared at this clinic. It is interesting and novel in several respects, and I am including it herewith.

Case 5.—A young man, who resided in Colombia, South America, three years previously. Swelling in scrotum of two weeks' duration. Diagnosis: lymphangitis, probably filarial. Excision. Apparent cure.

F. E., male, aged twenty-three years, was admitted for treatment May 23, 1933. The patient had been told he had tuberculosis of the testicle. There was no family history of tuberculosis. Three years ago, while living in Colombia, South America, the patient contracted gonorrhea, of which he was apparently cured, but afterward frequently had burning in the urethra. He left Colombia a few months later. Eight days ago the patient suddenly noticed a swelling "of the left testicle." He had had no previous swelling or pain in that region, and no urinary symptoms. He had never had hematuria or pain in the back, spine or abdomen. The pain in the testicle had persisted during the day, but he had been free from discomfort while in bed.

Examination.—W.B.C. 7,800, Hb. 100 per cent, B.P. 130/80, T. 99.2, R. 22. The patient was a well developed, rather small man. The spine was straight and percussion caused no pain. Abdominal examination was negative. Genitalia: There was a slight urethral discharge, which showed pus cells and many non-specific organisms; no gonococci. The right testicle, epididymis, cord and groin were negative. On the left side the testicle was negative. The globus minor and the body of the epididymis were negative. In the region of the globus major there was a hard mass 2 x 2 x 2.5 cm. in size. The vas was negative, but there was "some thickening of the cord." The prostate was slightly thicker than normal, but soft. The left vesicle was not palpable. The right vesicle seemed enlarged and slightly indurated; neither vas deferens was felt. Impression: tuberculous epididymitis, with involvement of the left seminal vesicle.

Urinalysis: acid, no albumin, sugar, casts or R.B.C., a few W.B.C., no infection; centrifugalized specimen negative for bacteria. Wassermann reaction and flocculation test were negative. X-ray of chest showed a small area of fibrosis in the left infraclavicular region opposite the first interspace anteriorly, which, although probably of tuberculous origin, was of questionable clinical significance; otherwise the lungs appeared clear.

On May 31 a cystoscopy was performed with Young's small catheterizing cystoscope. The bladder and prostatic orifice were normal.

Bilateral ureteral catheterization was done. The specimens of urine, obtained from both kidneys, were negative. Careful studies for tubercle bacilli were negative. Guinea pigs were inoculated. Stereo-bilateral pyelograms showed normal kidneys and ureters.

On June 5 examination showed the penis to be normal. The right

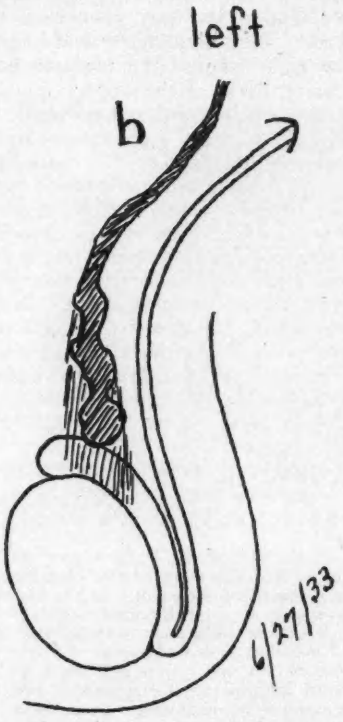

Fig. 12. Case 5. Chart made June 27, 1933, showing cord with three nodularities attached to the globus major of the left epididymis.

testicle, epididymis, cord and groin were negative. The left testicle was normal. At the upper portion of the epididymis there was a peculiar, markedly irregular mass, as shown in the chart (Fig. 12). As seen here, the induration does not involve the tip of the globus major, but seems to invade the remainder of the globus major for a distance of 1.5 cm. The mass measured 1.5 cm. x 1.5 cm. x 5 mm. The

upper portion was irregular, and ended in two cords, which continued upward as indurated cords (lymphatics?) adjacent to, but not within, the spermatic cord. At the upper end they were lost in the fat of the left groin and pubic region. They could not be followed into the external ring. The vas deferens was palpable from the epididymis to the external ring, apparently normal in size and consistence, and in no way connected with the indurated cords above described. The globus minor and body of the epididymis were negative. The right lobe of the prostate was normal in size, slightly indurated, particularly at the upper end, where there was a peculiar adhesion which ran upward and outward. The right vesicle was negative. At junction of the membranous urethra and prostate, there was a small area of induration. The upper portion of the left lobe was indurated, and from it indurated cords ran upward and outward a short distance over the lower portion of the left vesicle. The induration was quite superficial, and it was thought it might be between capsule and rectum. The left vesicle was soft in its upper portion, but lower down there was induration near the prostate which seemed to be "perivesicular rather than intra." Neither vas deferens could be definitely palpated. Impression: "I believe the prostate and vesicles are practically normal, and that the induration above described is perivesicular and back of the prostate. The case does not seem to me to be either tuberculous or gonorrheal in nature, but I believe the condition in the scrotum is similar to that found in Cases 1 and 2." (Young.)

June 11, 1933, the discharge note stated that the patient had improved and the swelling was much smaller.

June 24, 1933, a special note by Dr. Lewis read as follows:

"The globus minor of the epididymis is now very slightly indurated. The globus major feels normal and the body of the epididymis is palpable lateral to the vessels. In the spermatic cord, medial to the epididymis, and probably attached to the globus major, is a hard, round nodule 1 cm. in diameter. It is firm, almost third degree in induration. Above this nodular enlargement there is a constriction, and then a second nodule 0.5 cm. in diameter. Above this there is another constriction, and then a very small nodule, which continues upward as a fibrous cord anterior to the spermatic vessels. This hard cord can be palpated to the external inguinal ring. Impression: lymphangitis of the spermatic cord. An operation is advised by Dr. Young."

On June 28 operation was performed by Dr. Lewis. Under gas, oxygen and ether anesthesia through a two inch scrotal incision the tunica vaginalis communis was incised and the vas deferens located lateral to the mass in the spermatic cord. This was isolated immediately. The mass originated in the tunica vaginalis communis just medial to and above the globus major of the epididymis. A nodule 1 cm. in diameter was palpable above the globus major. Above this was a constriction, and a second nodule 5 mm. in diameter, followed by another constriction, and a third nodule 3 mm. in diameter, above

which a firm cord about 2 mm. in diameter extended anterior and external to the spermatic vessels. It was made up of several fine, fibrous looking structures, probably lymphatics. The mass and cord were excised up to the groin, as high as the external inguinal ring, without injury of the cord, epididymis or spermatic vessels. The epididymis appeared normal. The mass was readily removed from the tunica vaginalis. The hydrocele sac was everted and sutured posteriorly. Good hemostasis was obtained, the dartos and cremasteric fascia were closed with plain catgut and the skin with interrupted silk.

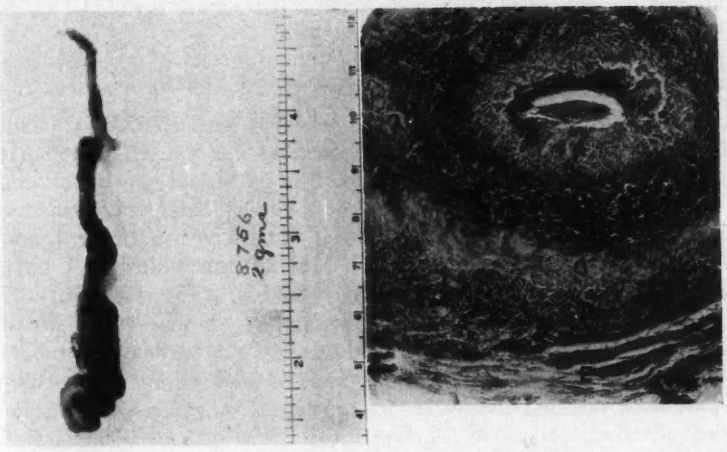

Fig. 13. Case 5 *(left)*. Photograph of specimen removed at operation.

Fig. 14. Case 5 *(right)*. Section of lymphatic cord: *a*, lumen lined with endothelium; *b*, zone of lymphocytic infiltration; *c*, fibrous sheath; *d*, second zone of lymphocytic infiltration; *e*, cremasteric fascia.

The mass removed was undoubtedly made up of a group of lymphatic vessels, which were coiled above the globus major. Secondary coils from the first formed the small nodularities.

Pathology.—The specimen was a round, firm cord 8 cm. in length, 2 cm. in diameter at its smallest end, and presented a bulbous enlargement 1 cm. in diameter at one end (Fig. 13). The tube was coiled. The bulbous enlargement presented four rounded portions bound together with fibrous tissue. On cross section we found that these rounded parts were coils of the cord above described. Sections of this cord showed a very tiny lumen through its center with walls 1 to 1.5 mm. thick.

Microscopic sections taken through the bulbous enlargement of the

cord showed in gross three sections of a tube, each presenting a double lumen. These tubules were bound together with fibrous tissue surrounded by fat and fascia. These tubules were lined with endothelium, the walls of which were infiltrated with round cells which did not extend outside the fibrous sheath of the tube (Fig. 14). No typical giant cells and no tubercles were seen.

Impression.—Lymphangitis, chronic, non-tuberculous, possibly due to filariasis.

The convalescence was uneventful, and the patient was discharged on July 9. The wound was well healed. Urine was acid, S.G. 1.026, no albumin or infection, and a few W.B.C.

ETIOLOGY OF THE FOREGOING CASES

For obvious reasons tuberculosis was first suspected as the cause of these four remarkably similar conditions, but when I found that the indurated cord, which passed up from the epididymis or testicle, was not the vas, but an irregular cord with globular enlargements, which lay external to the vas and veins of the spermatic cord, and beneath the skin, I discarded the idea of tuberculosis. I have never seen such a condition in tuberculosis. The fact that the entire vas, seminal vesicles and prostate were apparently normal, that the urine was normal, that there was no evidence of tuberculosis elsewhere in the body, and that repeated guinea pig inoculations with pus and tissues in the first case, and of tissue alone in the second, always gave negative results, fortified me in my belief that the disease was not tuberculosis. Direct smears and cultures were also negative for tubercle bacilli. The conclusion at the clinic was that tuberculosis had been definitely ruled out as an etiologic factor.

Syphilis was also considered. The fact that the testicle itself was not involved in any case was strong evidence against lues. The Wassermann reaction was negative in all cases, and the history gave no suggestion of venereal infection. In the second case intratesticular inoculations in rabbits were negative. Lues was therefore excluded as a causative agent.

Filariasis was strongly suspected in these cases from the beginning, as the patients came from Colombia, South America, which is the center of a very great filarial infestation of various types. In one case the history showed that several members of the family had suffered from filarial disease.

A search of the literature was then instituted at my request by Dr. J. N. C. Gordon, in order to find reports of similar pathologic conditions in proven cases of filariasis. Attention was particularly directed to reported cases of funiculitis, lymphadenitis and epididymitis. Tropical or climatic bubo was also considered—a disease which occurs in young white adult males in the tropics, and is characterized by inguinal lymphadenitis of a chronic nature, with complete absence of genital or venereal lesions, of which the causative agent has not been determined. Dr. Gordon tells me he has seen many of these cases in his work with the Navy in the tropics, and has never seen the epididymis involved. His study of the literature also shows no involvement of the epididymis or cord. Lillie[4] in a study of twenty-eight cases of climatic bubo has found a varied inflammatory pathology, but no evidence pointing to definite etiology.

Turning to filariasis Dr. Gordon found four forms which were considered most important:

1. Dracunculus medinensis (Guinea-worm) is a large worm, the female of which measures 20 to 30 inches in length. It is found in man lying in or migrating through the subcutaneous tissues of the arm or leg, and is often visible through the skin. It causes no lesion similar to those encountered in our cases.

2. Loa loa (Filaria oculi) is a much smaller worm 2 to 5 cm. in length, and about 0.5 mm. in diameter. It burrows beneath the conjunctiva, but causes no lesion in the genitalia or groin.

3. Wucheria bancrofti (Filaria sanguinis hominis) is the most widely known of all the filariæ. It is comparatively small, the female 7 cm. in length and the male 5 cm. It is found in Colombia. Its insect vector is a mosquito in which the parasites have been demonstrated. Man is the definitive host. The larvæ, or "microfilariæ," are found in the blood stream, but only at night. They cannot always be found.

Wucheria bancrofti causes a multiplicity of lesions in its human host, principally among which is elephantiasis, but lymph scrotum, varicose groin glands, lymphangitis and lymphadenitis, funiculitis and epididymitis also occur. In our cases, the glands were hard and were entirely different from varicose lymph glands, in which the lymphatics of the gland are varicosed by the presence of filariæ, and disappear when the patient lies down. Funiculitis has been

reported in the literature, and some of the cases were distinctly similar to ours.

Sorour[10] describes the pathologic findings in several cases of funiculitis. He describes the clinical picture as one of chronic nodular masses, varying in size from a hazel nut to a pigeon's egg, occurring in the spermatic cord. He gives no case reports, nor detailed microscopic descriptions, but mentions the fact that he found a heavy eosinophil infiltration inclosing thick walled blood vessels, whose lumina were partially or completely obliterated by organized thrombosis. Endothelial cell proliferation was marked. After an extensive study he was finally able to find filarial worms in all the cases, either in the form of an intact worm, or of degenerated worm inside a lymph vessel or filarial embryos in lymph vessels obliterated by endothelial and eosinophil cells, or of calcified remains of worms in the tissues. In old cases the eosinophil invasion is not found. The pathologic sections of our cases are thought by Dr. Gordon to agree very closely with those of Sorour.

Watanabe[11] has recently described ten cases in which filaria were found in lymphangitis in the spermatic cord. There were nodules in both epididymis and cord, and secondary enlargement of inguinal and femoral lymph glands, and generally a large or small hydrocele. The pathologic picture is described as an "exudative, degenerative, proliferative, and obliterative type of inflammation." Endothelial cells in large numbers were seen. Watanabe was able to demonstrate the presence of W. bancrofti in the lymph glands in all his cases, none of which is clinically exactly similar to our cases. Gordon did not consider any of his ten cases exactly similar to ours.

M. Longoria[5] describes a condition known as lymphotoxic funiculitis due to Filaria bancrofti, which can be generally demonstrated in the blood, but not always. He found the testis untouched in spite of the inflammation around it. A few cases went on to extensive suppuration, and some became firm, hard, chronic lesions.

Cerqua[2] states that the filariæ do not produce the changes directly as inciting organisms, but merely as foreign bodies. He cites a case of a smooth, firm enlargement within the scrotum, which extended up to the inguinal canal. The inguinal and crural glands on both sides were enlarged and painful. Complete orchidectomy was done and examination showed the tunica vaginalis indurated and filled with serous fluid. The epididymis and cord had been

transformed into a compact mass. The seminiferous tubules were markedly dilated some 0.5 cm. in diameter. They contained a creamy pus. Microscopically the epididymis consisted of connective tissue which was rich in vessels and thickly infiltrated with round cells and eosinophils. A filarial worm was found in the relatively uninvolved testicular tissue. Gordon considered that this case resembled our cases quite markedly. Cerqua thought that worms must have been in the epididymis and spermatic cord, but that they had been destroyed by local reaction and were no longer demonstrable.

Another form of filaria—onchocerca volvulus—is found very frequently in the northern portions of South America, and particularly in Colombia. Its wide dissemination is well described by Mohammed.[6] The female is 25 cm. long and viviparous. The microfilariæ are 250 to 300 mu. in length and are rarely found in the blood. The adult worms travel in subcutaneous tissues which are rich in lymphatics. The mode of transmission has been domonstrated to be by means of flies of the species Simulium, which is found in Colombia. The inguinal endocrural region, spermatic cord and epididymis are frequently the site of invasion of this parasite, which is also found elsewhere. Tumors are formed which vary in size from a pea to a goose egg and may be elastic or firm, and are due to the presence of a worm in a lymphatic vessel, which causes inflammatory reaction and resultant fibrosis.

Ouizellau[8] reported finding these tumors on the inner parts of the inguinal folds over the symphysis, and along the spermatic cord in the groin, where they can easily be confused with lymphatics. These tumors contain fluid, thin in early cases, thick and grumous in the older. He found embryos most common in the serum of the cyst, and also in the inguinal glands. He believes the tissue reaction is due to the presence of embryos.

Dubois[3] states that embryos could most often be found in the glands of the inguinal canal, but that he did not find them in the blood. This was confirmed by Montpelier.[7] Blacklock[1] states that larvæ could be demonstrated in the skin, whereas the picture of the glands was negative. Sharp[9] mentions the fact that the worms may become calcified or absorbed. The histo-pathologic picture of the nodules is described by the Harvard expedition as fibromata, which may or may not contain parasites. Around the parasite

there is usually a reactionary area made up of round, endotheloid, plasma cells and eosinophils. These may disappear later. Giant cells are not common.

Mohammed says that in onchocercous infestation tumors are always present, and in addition elephantiasis, glandular enlargements, skin lesions, erysipelas and eye lesions may occur. He believes the nodules are formed by the slow coiling up and uncoiling of an adult worm on itself, and a coincident tissue reaction around it, resulting in fibrosis and tunnel formation around the worm sections. As the disease progresses the fibrous tissue due to the worm toxins eventually produces a complete avascularity. This in turn leads to liquefaction of the worm, and formation of cysts and abscesses containing the digested worms. This accounts for the absence of the worm in chronic nodules, and the fact that the eosinophils, which are present early around the live worm, gradually disappear.

CONCLUSIONS

Five cases have been reported, four of which are quite similar, and one an ordinary case of chronic epididymitis, which occurred following cystoscopy, and is presented to contrast with the other four cases. This patient came from the same locality in Colombia, South America, but presented entirely different lesions.

The first three cases and the fifth, which have been cited in detail, are remarkable in that the disease did not start in the testicle, epididymis, vas or vessels of the cord, but as a peri-testicular or peri-epididymal disease. It was characterized by the ultimate formation of a very dense mass of tissue, which in two cases has completely enveloped and compressed the epididymis without involving the tissues of the epididymis at all. From its point of onset in the coverings of the epididymis or testicle, the disease has always travelled upward outside the spermatic cord more or less loosely attached to the external fascia of the cord; in some instances forming large globular masses, and in others, very fine lines, suggesting lymphatics with small, bead-like enlargements along the course of the lymphatic. The presence of enlarged inguinal glands has been notable. In none of the tissues removed, have we been able to find any evidence of any ordinary bacterial inflammation, nor of tuberculosis, syphilis or malignant disease. The pathologic process is

characterized particularly by the deposit or growth of large numbers of round cells, which have ultimately gone on to the formation of a marked fibrous sheath or covering. The tunica vaginalis in some instances has been very extensively involved with adhesions to the testicle, but the testicle itself has been free from disease, although compressed and distorted by the fibrous tissue in one case. The intrascrotal cord produced by the disease has been characterized also by the presence of much vascularity and around the walls of the blood vessels are numerous areas of round-cell infiltration. There are spaces which may be lymphatics, but they contain no material in the stained sections, and nothing suggesting either a large or a small worm or larvæ, or detritus resulting from the presence of a dead worm, has been found. Nevertheless, it seems to us evident that the disease is filarial in origin. In the first case the numerous enlarged glands in various parts of the body in a man who had no evidence of syphilis is very suggestive of filariasis, and in the second case the presence of filaria in several members of the family, going back a generation or more, is presumptive evidence that this disease is the etiologic factor. It is possible that it may be due to some remarkable process which has not been described before, because of the fact that nowhere in the literature have we been able to find exactly the same conditions present as have been found in these cases, and no filaria were discovered. Regardless of this, we are inclined to believe that the disease is due to filaria, and that the onchocerca volvulus is probably the causative factor. Our experience shows that radical surgery should be applied in these cases, as the results obtained have been very satisfactory.

My sincere thanks are due to Drs. Dumbauld, Gordon and Lloyd Lewis who have given much time to the study of the pathology and literature of this interesting disease, and without whose assistance this paper could not have been prepared. Much of the data and conclusions are the results of their studies.

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BACTERIOPHAGE IN GENITO-URINARY TRACT INFECTIONS

JOSEPH F. McCARTHY, M.D., and (by invitation)
J. SYDNEY RITTER, M.D.

From the Department of Urology, New York Post-Graduate Medical School, Columbia University, New York

As clinicians our interest in whether bacteriophage, as contended by d'Herelle, is a living ultra-microscopic being, a ferment, or lytic substance, as believed by others, is largely academic. Our real concern is what it can do in the alleviation or eradication of disease and how it may best be administered. Neither should we confuse a fact finding communication on this subject with abstruse problems of natural and acquired immunity. It is interesting to note that though much has been written on this subject, comparatively little in the way of clinical experience in the treatment of the genito-urinary tract infections has been reported.

Some three years ago, in collaboration with Dr. Ward J. MacNeal, Director of the Department of Pathology and Bacteriology, and through the support in part by a fund from the Joshua Macy, Jr., Foundation, we have been engaged in the clinical application of bacteriophage in this field. In this study our procedure has been somewhat as follows.

At first an aseptic specimen is obtained. Our practice has been to employ the customary sterile catheter, though our bacteriologic collaborators have proven to their satisfaction that under the methods of external preparation as outlined by them, it is feasible to collect specimens of urine both from male and female patients, uncontaminated by adventitious bacteria. One determines whether there be a mixed, dominant, or a pure culture. Then follows the preparation of a specific bacteriophage when this is possible.

In the interim the patient is subjected to a complete urologic survey, as it is of the utmost importance to ascertain the site and extent of the infectious process, as well as the presence or absence of urogenital obstruction, congenital malformation, functioning activity, et cetera. Such conditions as malposition of the kidney, calculous disease, angulation, distortion or stricture of the ureter,

TABLE I. ANALYSIS OF 293 CASES REFERRED FOR BACTERIOPHAGE THERAPY

Bacteria	Bacteriophage obtained	Bacteriophage not obtained	Sterile
B. coli (undetermined)	6	4	
B. coli communior	20	12	
B coli acidi lactici	66	13	
Streptococcus viridans	0	2	
Bacillus pyocyaneus	3	3	
B. coli aerogenes	0	29	
Bacillus proteus	4	4	
Staphylococcus aureus	10	1	
Gamma streptococcus	0	2	
Bacillus alkaligenes	0	2	
Staphylococcus albus	2	3	
Bacillus para coli	0	4	
Staphylococcus non-hemolyticus	0	1	
Streptococcus non-hemolyticus	0	3	
Staphylococcus hemolyticus	0	1	
Streptococcus hemolyticus	0	4	
Mixed infection	0	7	
Alpha streptococcus	0	1	
Unidentified coccus	0	1	
Sterile specimens			85
TOTALS	111	97	85

TABLE II. CONDITIONS IN WHICH BACTERIOPHAGE WAS OBTAINED

Seminal vesiculitis and prostatitis	8
Pyelitis	73
Ulcerative cystitis and pyelitis	3
Ureteral transplantation	4
Wound infection	2
Pyelonephritis	3
Septic thrombosis and pyelitis	1
Cystitis	13
Perinephritic abscess and carbuncle	1
Inoperable carcinoma of bladder	1
Stricture	1
Septicemia	1
TOTAL NUMBER OF CASES	111

vesico-renal reflux, vesical neck obstruction, urethral stricture, etc., should of course be recognized and corrected.

The interesting problem then arises as to whether one should correct such lesions immediately or suspend active interference pending bacteriophage therapy. It is our belief that in most instances, the infection should be attacked at once with the view to diminishing or removing the infectious process, and later, correc-

tion of the underlying condition should such be found. Having located the site of disease and urogenital status, in the absence of deformity or other anomaly, the patient is ready for bacteriophage therapy.

We must now consider methods of application. The first essential is the regulation of the hydrogen ion content of the urine to the point where bacteriophage is most effective. For the Bacillus coli group, an approximation of neutral or slightly alkaline is desir-

TABLE III. ANALYSIS OF THE USE OF BACTERIOPHAGE IN 111 CASES

	Poor result	Died	Organism resistant after treatment	Symptomatically improved bacteria still present	Cured	Secondary organism
B. acidi lactici	10	0	2	14	14	2
B. proteus	2	0	0	0	0	0
B. Coli undetermined	1	0		1	0	0
B. coli communior	2	0	1	8	4	0
B. pyocyaneus	1	0	0	0	0	0
Staphylococcus areus	0	1	0	1	4	0
Total	16	1	3	24	22	2

CASES EXCLUDED FOR THE FOLLOWING REASONS

Carcinoma of bladder	1
Negative before bacteriophage was used	9
Not sufficient data obtained	19
Failed to return for treatment	14
TOTAL	43

able. This is accomplished by potassium citrate, fruit juices, et cetera. It has seemed advisable to us to exercise hospital control of these patients during active treatment.

The bacteriophage may be administered by mouth, subcutaneously, intravenously, intravesically, and by way of the renal pelvis, or any combination of these routes. d'Herelle believes the best results are obtained in the presence of pyelitis, when the bacteriophage is instilled into the renal pelvis. This seems to have been substantiated in some of our cases. Some of our laboratory associates,

however, are of the opinion that this step is frequently unnecessary, inasmuch as the bacteriophage has been recovered from the urine in some instances, following subcutaneous and intravenous injection. Moreover, one should recognize the ever present possibility of the introduction of adventitious bacteria incidental to instrumental manipulation.

CASE REPORTS

Case 1.—J. S. B., was referred for treatment of perineal fistula October 23, 1931. Two years ago he was operated on at the American Hospital, Paris, for a prostatic abscess. The wound did not heal completely. A perineal fistula remained. An indwelling catheter was inserted and left in position for eight weeks. The fistula closed, but re-opened fourteen months later, and remained open.

The urine was hazy with pus. Culture: showed B. coli lactici, susceptible to bacteriophage.

Bacteriophage therapy consisted of six instillations into the bladder and six subcutaneous injections. In ten days, this patient was free of symptoms and negative to every known clinical and laboratory test. The perineal wound closed. Culture of the urine showed no growth. At the date of this writing the patient remains well.

Case 2.—S., aged fifty-two years, was operated upon for a left renal calculus. Postoperatively the wound was profoundly infected. Culture of the pus grew a staphylococcus aureus. An active bacteriophage was obtained. Bacteriophage therapy consisted of four injections subcutaneously, 1 c.c. bacteriophage and 10 c.c. applied to the wound. After this treatment, the wound showed immediate and spectacular improvement and rapid healing ensued.

At this time the patient complained of dysuria and burning on micturition. Culture of the urine showed the same organism and again bacteriophage therapy was instituted, consisting of bladder irrigations of 30 c.c. and subcutaneous injections of 1 c.c. on three successive occasions. After the third injection, the urine was cleared. However, burning persisted and 10 per cent argyrol was instilled into the prostatic urethra on two successive occasions. The patient left the hospital, free of all evidences of this infection.

Case 3.—J. Diagnosis: septic thrombosis. Organism found, B. coli communior on blood culture taken June 6, 1927. Intravenous injection of anti-colon asparagin bacteriophage was given on August 1, 2, 3, and 4. Following inoculation of bacteriophage, the patient's symptoms improved and temperature approached normal. Urinary symptoms persisted because of the patient's objection to local therapy. Attempts were made to regulate the P_H concentration of urine, but the patient left the hospital.

Case 4.—Dr. N., aged sixty-three years, came for treatment of pyuria and dysuria. Two years prior to reporting to our clinic, a prostatectomy was performed upon this patient. Examination of the prostato-seminal secretion revealed B. coli communior. An active bacteriophage was obtained. The patient was treated by subcutaneous injections and instillations into the prostatic urethra together with massage of the prostate and seminal vesicles. The patient's condition improved symptomatically after one month's treatment.

Culture was taken. The B. coli communior were not found. However, B. pyocyaneus made its appearance. Bacteriophage was obtained which was active against the B. pyocyaneus, and treatment was instituted as previously mentioned. Following one month's treatment, culture showed the absence of the B. pyocyaneus and a recurrence of the B. coli communior, which organism was again susceptible to the bacteriophage. The patient was then treated with a combined bacteriophage and showed marked improvement for about two months, after which time cultures were made and both organisms were again recovered. Direct instillation of bacteriophage into the seminal vesicles was suggested. However, the patient did not return for further treatment.

Case 5.—C. H., aged thirty-four years, was admitted to Post-Graduate Hospital on June 29, 1931, complaining of vaginal bleeding. This was accompanied with considerable pain and temperature. When admitted, temperature was 102°, pulse 118, respiration 20. General physical examination was essentially negative. Local examination revealed a large cystic swelling in the lower abdomen which on vaginal examination was extremely tender in the region of the posterior cul-de-sac.

Posterior colpotomy was performed and a large quantity of pus evacuated. Culture of this pus showed Streptococcus viridans.

The temperature continued to take a septic course. Ten days after the first operation, an abdominal exploratory operation was done. At this time an infected papillary cystadenoma of the ovary was found, but not completely removed. An intestinal fistula followed and, because of the patient's condition, repeated transfusions were given. The patient's temperature continued a septic course. A mixture of coli, staphylococcus, pyocyaneus, bacteriophage was injected into the wound. Following this, the wound healed promptly. However, the septic temperature persisted. Upon culture of urine which contained many pus cells, bacteria coli communior susceptible to bacteriophage was found. Potassium citrate was given so as to prepare the PH concentration of the urine for bacteriophage therapy. On August 4, or three and one-half weeks after the second operation, bacteriophage therapy was begun. Bacteriophage was instilled into the bladder in 10 c.c. amounts every day for three days. Then an interval of three

days elapsed and one more instillation was given. During this time, several hypodermic injections of 0.5 c.c. bacteriophage were given.

Following the use of the bacteriophage, the temperature immediately began to drop and reached normal eight days later, the first time since admission to the hospital. It remained practically normal for the next seventeen days, at the end of which time the patient was discharged from the hospital apparently cured.

Case 6.—M. H., aged twenty-seven years, was admitted to the New York Post-Graduate Hospital complaining of pain in the left renal region together with chills and fever. Flat x-ray exposure showed two calculi in the pelvis of the left kidney. Indigo-carmine renal function test showed a normal right kidney. There was no dye from the left side. However, a definite stream of tooth-paste-like pus was seen exuding from this orifice. A culture of the left kidney urine showed a Staphylococcus aureus, susceptible to bacteriophage. A ureteral catheter was left in the left ureter for drainage purposes, and on obtaining a potent bacteriophage, 10 c.c. was injected through the ureteral catheter and 1 c.c. of the asparagin bacteriophage was injected intravenously at 2:00 and 4:30 P. M.

Early the following morning, 10 c.c. of bacteriophage was injected through the ureteral catheter and the patient was operated on. At the time of operation a fairly good kidney was found. It was, therefore, thought advisable to try to save this kidney. The wound was walled off with bacteriophage-soaked gauze prior to opening the renal pelvis. Instead of the pre-operative thick purulent material, there was observed a small amount of translucent fluid. Both calculi were removed and in order to favor drainage, a large ureteral catheter was left in position and for counter-drainage. A nephrostomy was made and a winged catheter inserted through this wound into the renal pelvis.

Post-operatively the renal pelvis was irrigated with 10 c.c. of bacteriophage and 1 c.c. injected subcutaneously daily. On the eighth postoperative day, this patient developed a lobar pneumonia. Nevertheless, on doing an indigo-carmine renal function test on the twelfth day following operation, the dye appeared in three minutes in good concentration from the left kidney. The pneumonic condition subsided and the patient was discharged from the hospital about one month after admission.

Two weeks after leaving the hospital, a sterile bladder specimen taken showed no Staphylococcus aureus to be found.

Case 7.—C. K. was admitted to the New York Post-Graduate Hospital with a history of having had some boils about two weeks prior to admission. The patient had been running a septic temperature with definite evidences of pneumonia.

On culture of the sputum and area where one boil was still present, Staphylococcus aureus was found. A blood culture was done which

also showed the Staphylococcus aureus. The patient was therefore treated with bacteriophage, intravenously, subcutaneously and by local application. His condition improved and after his temperature had remained normal for about one week, he complained of pain in the left upper quadrant.

Careful examination relative to pleurisy was made and found to be negative. Urine, upon examination, contained many pus cells. Culture showed Staphylococcus aureus. After a urologic examination, a diagnosis of pyelitis and perinephritis was made.

This patient was operated upon and the perinephritic abscess drained. At the same time bacteriophage was injected into the cavity. This patient was treated with bacteriophage locally through the wound and by pelvic lavage as well as subcutaneously. It seemed for a while that the condition was under control. However, the patient's temperature returned to the septic type, he was acutely ill, and due to the suspicion of there being a cortical abscess of the kidney, a secondary exposure was done. At this time the entire kidney was involved and removed. It was necessary to make a blood transfusion.

The pathologist reported a carbuncle, involving the entire kidney. The patient was about to be discharged from the hospital when he had an attack of pyuria, dysuria and hematuria, together with pain on the right side. A large tumor-like swelling could be seen filling the right upper quadrant. On palpation, this was definitely recognized as the right kidney. Pain was severe as was also acute tenderness on palpation. Diagnosis at this time was nephritic abscess in the sole remaining kidney. We had given up hope, for it seemed that the right kidney was involved to as great an extent as the left kidney had been. The patient was then put on intensive bacteriophage therapy intravenously and intrarenal pelvically, and after several months left the hospital.

This patient was instructed to take bacteriophage by mouth over an indefinite period of time. He was seen one year later, at which time the urine showed a few pus cells. There were no bacteria on culture. It is three years since his last operation, but there is still some pus in his urine. He has meanwhile gained 100 pounds.

Case 8.—L. S., aged five and one-half years, reported to the New York Post-Graduate Hospital complaining of pain in the left upper quadrant. General physical examination was negative.

Cystoscopic examination revealed a normal appearing bladder. Indigo-carmine function test showed both sides normal. Urine from the left kidney contained pus and Bacterium acidi lactici which was found susceptible to bacteriophage.

The patient received instillations of bacteriophage into the left renal pelvis and subcutaneous injections. After a month's treatment, symptoms subsided.

One year later, the patient returned with similar symptoms. The same organism was recovered from the left kidney. A pyelogram at this time showed definite dilatation of the left renal pelvis. Bacteriophage therapy was instituted. The urine has remained sterile up to date, which is over a year since the last treatment. This experience demonstrated the necessity for repeated follow-up.

Case 9.—T., whose complaint is septic temperature, dysuria, pyuria, of one week's duration, has been at the New York Post-Graduate Hospital with an osteomyelitis for some time. About one week ago his temperature began assuming a septic curve and the patient complained of frequency, and burning urination.

Culture of the urine showed a B. coli acidi lactici, susceptible to bacteriophage. The patient was therefore placed on bacteriophage therapy. He was given subcutaneous injections and direct lavage of each kidney. At the first treatment the left kidney was found to be the source of infection, the urine from the right kidney being normal. After the first pelvic lavage, this patient's appetite returned and his general condition improved. He was given four treatments; the first, as described above; second and third, subcutaneous injections and bladder instillations; the fourth, given three days later, was an intra-pelvic instillation of the left kidney. Temperature returned to normal and the patient's general condition showed marked improvement. He left the hospital free of all urinary signs or symptoms.

Case 10.—J. S., aged four years, was admitted to the New York Post-Graduate Hospital with a history of persistent pyuria over a period of two years. Physical examination was essentially negative.

Cystoscopic examination showed a fairly normal bladder with some edema around both ureteral orfices. Specimens of urine obtained from the separate kidneys were sent to the laboratory. B. coli communior was recovered and bacteriophage therapy instituted. This patient did not respond to intravesical and subcutaneous injections of bacteriophage. An intravenous urogram demonstrated a double ureter on the left side. Our reaction to this case is that treatment directed to the renal pelves might have given a better result.

Case 11.—J. E. D., aged fifteen years, was admitted to the New York Post-Graduate Hospital, complaining of pyuria and a history of having had pyelitis with chills, fever, pain. This child has had repeated attacks during the past five years.

Cystoscopic examination revealed a large dilated right ureteral orifice. The left appeared normal. A specimen of urine was obtained from the separate kidneys. From the right kidney a culture of B. coli lactici was obtained. This child was treated with bacteriophage instillations into the bladder, right renal pelvis, and subcutaneously. After several months' treatment, a culture taken of the bladder urine showed many colonies and at this time specimens obtained from the separate

kidneys showed about 200 colonies of bacteria per c.c. from the right kidney, none from the left. Intravenous urographic study showed a small right kidney, the renal pelvis and calices dilated.

An airogram demonstrated a reflux up the right ureter, which is definitely dilated.

Deduction: When such an anomaly as vesico-renal reflux is present, little may be expected by way of this form of therapy until the basic condition is corrected.

Case 12.—A. P. was referred from the Pediatric Clinic, New York Post-Graduate Hospital, complaining of pyuria. This child's general condition was subnormal and her mother brought her to the hospital for building-up.

On examination, many pus cells were found in the urine. Catheterized bladder specimen was taken and sent to laboratory for bacteriophage study. The B. coli acidi lactici was found and this strain was susceptible to bacteriophage. The patient was, therefore, given 10 c.c. of bacteriophage instilled into the bladder and 0.5 c.c. subcutaneously. There were only five injections given over a period of one month due to the lack of coöperation on the part of the patient. One month later, a second attempt was made to have the patient report regularly to the clinic, and at this time 2 c.c. of bacteriophage was given subcutaneously and 10 c.c. instilled into the bladder. After four injections the number of organisms dropped from 1,260,000 bacteria per c.c. to 16,000. For various reasons, a complete urologic examination was not done on this child and in March of this year, an intravenous urographic study and pyelogram were made. Prior to this, a sterile specimen of urine was sent to the laboratory for bacteriophage and the organism was found to be resistant to bacteriophage.

Intravenous urogram revealed a poor functioning left kidney with a large pyonephrosis. Retrograde pyelogram showed a distinct obstruction at the uretero-pelvic junction. A nephrectomy was performed.

This case demonstrates the importance of a complete urologic study prior to instituting this form of therapy, as well as the coincidental correction of the underlying disease factor.

When it is remembered that prior to the advent of bacteriophage therapy by the methods at our disposal, the results have been either negligible, or at best the course of the disease has been long continued, with repeated painful and painstaking instrumental treatments, it becomes at once obvious that here we have a method which marks a distinct advance in the management of these intractable lesions—a most hopeful augury for the future. In any event, we assert without fear of contradiction that we have salvaged a number of lives by the use of this agent, wherein no

other method of which we have knowledge would have availed.

Finally, it is routine practice with us to seek a specific bacteriophage wherever urinary infection is encountered.

SUMMARY

In a consideration of this still undeveloped field of clinical activity, it seems to us desirable, first to evaluate actual results, and by way of enlisting the collaboration of other clinical centers, to speculate a bit on its possibilities.

Under the first heading it should be emphasized that in each instance only a specific bacteriophage has been employed. In all probability, the general failure to exercise this precaution has resulted in a complete misapprehension of the clinical potentiality of this agent.

A complete urologic survey is a necessary prerequisite. Competent laboratory supervision, not only in the preparation of the bacteriophage, but also of the individual case, to the end that there be maintained a close interlocking of the two departments; supplemental correction of underlying pathology or anomaly as well as the search for and care of remote foci.

In this series, 293 cases were referred for bacteriophage therapy. Of these, bacteriophage was obtained in 112 cases. Definite data were secured in sixty-nine cases, and forty-three were excluded for the following reasons:

Carcinoma of the bladder	1
Negative before phage was used	9
Not sufficient data obtained	19
Failure to return for treatment	14

Data secured on the 69 cases gave the following information:

Negative result	16
Resistant after treatment	3
Symptomatic improvement (not bacteria-free)	24
Symptomatic and bacteriologic cures or 36+%	25

In 16 cases of Staphylococcus septicemia, most of which were cared for in other departments of the hospital, there have been six recoveries under bacteriophage therapy—an extraordinary record in so grave a condition. Our most spectacular results were noted in patients acutely ill. It should be noted here, however, that in a certain percentage of cases of apparent cure, later cultures of the same or other bacteria have been developed.

FUTURE POSSIBILITIES

Aside from the preceding, it seems to us as altogether likely that the immediate future will reveal such advantages as:

1. The prevention of kidney infections that occasionally eventuate from carbuncle or furunculosis by the prophylactic administration of a specific bacteriophage where such is obtainable.

2. Where bacteriophage therapy is feasible, in the presence of infectious calculous disease, pyelonephritis, et cetera, it seems to us as probable that radical operative intervention in such cases should be deferred pending attempts at pre-operative sterilization of the infectious process by preliminary intra-renal pelvic and other modes of administration of this substance.

3. We have devised instrumental measures for direct intra-prostatic administration as well as injection into the seminal vesicles.

Finally, to the end that a precise evaluation of this method in a large number of cases may be had at an early date, and with the realization of the necessity of accurate technical data, our experience in this field is at the disposal of our colleagues.

A STUDY OF COMPARATIVE EFFECTS OF VARIOUS HIGH FREQUENCY CURRENTS AND OF THERMAL CAUTERIZATION IN PROSTATIC RESECTION

JOHN R. CAULK, M.D., F.A.C.S., and (by invitation) WILBUR HARRIS

From the Genito-urinary Section of the Department of Surgery, School of Medicine, Washington University, St. Louis, Missouri.

The results of the cautery punch operation have indicated to one of us (J. R. C.), for a number of years, that transurethral surgery should occupy an important place in the treatment of prostatic obstruction. It is gratifying to observe the tendency for urologists at the present day to adopt this type of surgery in an increasing percentage of cases. There is a decided inclination to employ various types of high frequency currents for the technical extraction of the tissue.

In many instances these various currents have been used promiscuously, the operators having been led to the belief that they possessed no dangerous qualities, that they were practically harmless. Most of us have been fascinated by the manner in which tissue can be removed by high frequency resection, but few have stopped to analyze any of the inherent potential dangers in the manipulation of these high tension currents and most of us have been entirely ignorant of their physical characteristics. It was only after a late secondary hemorrhage or a severe urinary sepsis, or some other unpleasant sequel of an operation which had gone nicely, that we began to pause and wonder what breach of technic had been responsible for this consequence. We had been told by the manufacturers that there was no heat except at the site of burn. It was therefore supposed that something in the manner of manipulation, too much coagulation or too great a rapidity of the strokes had been responsible for this eventuality. Usually, however, a satisfactory explanation was not at hand.

It seemed, therefore, propitious that a more thorough knowledge of the fundamental workings of these currents in tissue be undertaken. To this end we are presenting an experimental and clinical study of the effects of actual cauterization and of the va-

rious high frequency currents on experimental media, animal and human tissue, with the hope that the knowledge gained by this study will help to safeguard this important phase of surgery.

EXPERIMENTS ON GELATIN

In order to study the heating effects of high frequency currents in a homogeneous conducting medium, gelatin which contained

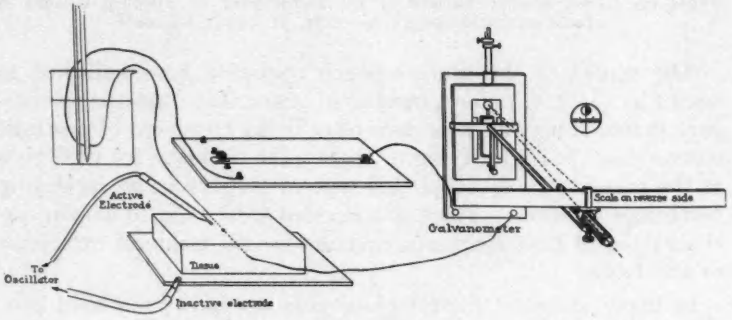

Fig. 1

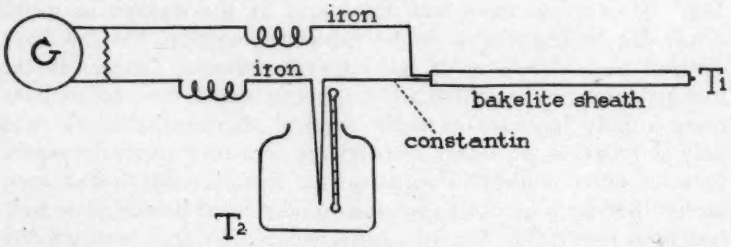

Fig. 2

0.95 grams of sodium chloride per liter was used. Blocks of gelatin were placed on a sheet of tin which served as an indifferent electrode, while the active electrode was applied to the upper surface of the block (Fig. 1).

The temperature measuring device consisted of the well known thermocouple, galvanometer combination. The couples used were made of two segments of iron wire with a segment of constantin wire interposed. This combination gave about 50 microvolts per

TABLE I. TEMPERATURES PRODUCED IN GELATIN WITH THE HIGH FREQUENCY CURRENT

S_1	S_2	Temperature change	Time Seconds	Distance from cutting loop to thermocouple	Current Value
8	28	1.21°C	3	1.5 cm	900 M. A.
	34	1.69	3		
	38	1.94	3		
	53.5	2.84	3		
	59.5	3.35	3		
	68.8	3.95	3		
	75	4.36	3		
	86	4.94	3		
	91.8	5.47	3		
	99.2	5.92	3		
	105	6.31	3		
	113.5	6.87	3		
	122.8	7.48	3		
	127	7.74	3		
	134	8.10	3		
	139.8	8.58	3		
	145	8.92	3	Interval between current applications equa'ls 10 seconds.	

degree difference in temperature between the junctions, which was sufficient to give full scale deflection on the galvanometer (sensitivity 6×10^{-8} amp. per div.) for 11 degrees centigrade difference in temperature between the junctions. In actual use the sensitivity was adjusted by using resistances in series and as shunts. It is advisable to use a shunt for the sake of galvanometer damping unless the instrument is already highly damped. The thermocouple junction that was to be placed at a point whose temperature fluctuations were to be measured was the point of a bakelite needle which

incased the iron and constantin leads. This needle was about 15 centimeters in length and 1.5 millimeters in diameter (Fig. 2).

Table I shows a sequence which is similar to operating conditions in some aspects. There was no circulatory system to serve as a cooling device, and the intervals between current applications

TABLE II. COMPARATIVE TEMPERATURE CHANGES OF HIGH FREQUENCY AND THERMAL CAUTERY IN GELATIN

Time Seconds	Distance	Temperature change °C	
		High frequency	Thermal cautery
3	.8 cm	3.21	0
		5.70	0
		7.80	0
		8.65	0
		10.10	0
		11.17	.001
		13.20	.003
			.120
Current values 500 M. A.			.214
Interval between current applications 10 seconds			.354
			.502
			.708
			.915
			1.158

are generally longer than ten seconds. However, it was necessary to allow water to drip on the gelatin at the active electrode to keep the crater, which it melted out, filled up so that the electrode made contact with the gelatin. S_1 is the initial galvanometer reading; S_2 is the reading after the current application; D is the distance from the active electrode to the thermocouple. Current was switched on for three seconds at a time, with ten-second intervals between. The amount of current passing through the gelatin was 900 milliamperes. The table shows the rise in temperature in a

sequence of applications of current at a depth of 1.5 cm., with little cooling.

Table II is a typical comparison of depth heating produced by the high frequency surgical apparatus and cautery. The heat conductivity of gelatin and similar substances is small. Table III

TABLE III. COMPARATIVE TEMPERATURE CHANGES OF HIGH FREQUENCY AND THERMAL CAUTERY IN GELATIN

Time Seconds	Distance	Temperature change °C	
		High frequency	Thermal cautery
3	0.4 cm	8.67	0
		19.15	0
			0
			.189
Current value 900 M. A.			.610
			1.464
			1.953
			2.440
			2.930
			Punch was heated from 3.5 volts.

again shows these relations, the temperature fluctuations being measured at a point 0.4 cm. directly below the point of application of the electrode or the hot blade, as the case may be. These sequences are the results of applying cutting current or the hot cautery blade three seconds at a time with ten-second intervals between applications, all other conditions being identical. The value of the high frequency current was 900 milliamperes. The active electrode was a sphere 0.5 cm. in diameter, and was submerged in the gelatin for Table II. The thermocouple was 1.3 cm. below the surface of the gelatin, or 0.8 cm. below the spherical electrode.

The comparison of the heat produced at different distances from the surface with high frequency and cautery applications is admirably represented in Tables II and III. The first reading in

Table II at 0.8 cm. below the point of application shows an increase of 3.21 degrees, and there is a gradual rise up to 13 degrees centigrade after seven applications, whereas with the cautery, temperature change was not detected for the first five applications and only .003 after a corresponding sequence of seven applications.

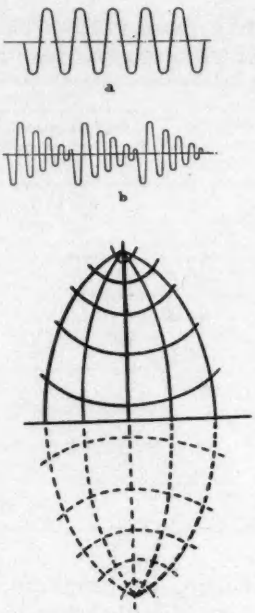

Fig. 3

It required fourteen applications before a degree of temperature could be registered at 0.8 of a C.

In Table III at a distance of 0.4 cm. from the point of application, the first three-second application caused a rise of temperature of 8.67° and the second increased the temperature to 19.15, whereas it took nine applications of cautery for the same application time to register 2.9 degrees.

The work of Robert Heller[3] with short waves on gelatin seems to indicate that when the waves pass between a point elec-

trode and a plate electrode they spread out in a conical configuration. It has been found, however, that the currents do not spread in conical or pyramidal forms exactly in homogeneous media. If this were true, temperature rises would be governed by the following relation:

$$T=\frac{kI^2t}{D^2}$$

where T is the change in temperature, t is the time of current flow, I is the current, and D is the distance from the active electrode to the point at which the temperature changes are to be

TABLE IV. TEMPERATURE RISE PRODUCED IN BEEF HEART TISSUE BY CUTTING CURRENTS

Aveage temperature rise for one 2 second stroke	Number of strokes at 20 second intervals	Increase in temperature during sequence	Current in milliamperes	Distance of thermocouple below active electrode
0.6°C	8	4.1°C	520	1.6 cm
1.2	12	12.0	520	1.2
1.9	8	14.6	520	0.8
5.8	6	13.3	520	0.5
18.3	1	18.3	520	0.3

measured. This would make the temperature change proportional to the time, the square of the current, and the inverse square of the distance for any point in the cone. Actually, the values are higher than the above formula gives for points along the direct line between the active electrode and the indifferent plate, and lower than the formula indicates near the edge of the cone. Figure 3 shows the approximate form of the streamlines of current and the equipotential lines. The paths of currents in other than homogeneous media may be very different, as the body of an animal, for example.

EXPERIMENTS ON MEAT

In these experiments the technic was the same as that used in studying temperatures produced in gelatin, and the results were

similar. Here again the aim was to duplicate operating conditions as nearly as possible. Samples of meat were placed on the indifferent electrode and cutting was done with a minimum current value on a constantly wetted surface.

Table IV shows some results on heart tissue, cutting on the septum, with the thermocouple inserted in the septum near the outer wall. In the table each line from left to right constitutes one body of data; for instance, the third line tells us that with

TABLE V. TEMPERATURE RISE PRODUCED IN BEEF HEART BY CAUTERY

Average temperature rise for one 2-second stroke	Number of strokes at 20-second intervals	Increase in temperature during sequence	Distance of thermocouple below hot cautery
.053°C	10	0.53	1.6 cm
.093	12	1.10	0.8
.189	11	2.07	0.4
.416	6	2.49	0.2

a cutting current of 520 milliamperes applied two seconds at a time and at twenty-second intervals, the temperature was raised 1.9 degrees centigrade each application at a point 0.8 cm. below the cutting. Further, it tells that in all eight cutting strokes were made (at twenty-second intervals) at the end of which time the temperature increase was 14.6 degrees above the temperature at the beginning of the sequence. The rise in temperature is less than eight times the increase for one stroke because of cooling. Here we do not have operating conditions duplicated, in that blood flow would increase the cooling effect. With blood flow, the time of cooling of the affected region is from two to five minutes, as will be shown later, but is faster than in the above case.

It should be noted that the applications of current lasted only two seconds each, whereas, in operations they require from four to twelve seconds, averaging from six to eight seconds in the operations observed. One eight-second stroke, with conditions as stated in the third line of Table IV, caused an increase of 15.7 degrees centigrade.

Table V shows results for conditions exactly analogous to those

for Table IV except that the cautery punch was used instead of high frequency machine. Attention should be called to one result not shown in the Table: The second line, for example (compare with the third line of Table IV), shows a 1.1 degrees increase in temperature 0.8 cm. below the hot blade (actually cutting) after twelve applications. The part not shown is the fact that no temperature increase was detected during the first five applications and intervals. This is a demonstration of the fact that the heat

TABLE VI. TEMPERATURE RISE PRODUCED IN LARGE PIECE OF BEEF (16 cm. thick) BY CUTTING CURRENT—WATER RUNNING

Temperature rise	Duration of cutting stroke Seconds	Distance from cutting loop to thermocouple	Current value
1.33°C	8	2.8 cm	680 M. A.
5.68	8	1.9	680
11.04	8	1.5	680
8.80	8	1.7	620
32.56	8	0.5	680

conductivity of tissue is surprisingly small. The time required for enough heat for detection to be conducted 0.8 cm. was ten seconds. For greater distances the time was longer.

Table VI shows results for individual eight-second cutting strokes. The last two determinations were not made on the same sample or with the same instrument settings as the preceding ones. The temperature at the actual point of cutting is between 500 and 600 degrees. This was determined by cutting with a wire loop which was a thermocouple. The same result is also reported by Ward, which is a well understood physical principle. Conductivity from the surface does not affect these values. The spread of current at that point is in all directions for a short distance, after which the flow of current assumes the form shown in Figure 3. Thus the temperature within a millimeter of the electrode goes much too high to be measured with the apparatus used here, and the measurements for slightly greater distances were made for short intervals of current flow. In Table VI the cutter was kept

moving and actually cutting to prevent charring the area near the active loop.

The analogy to Table VI using the cautery has no meaning, because the column of temperature rises would be zero in each case. The high frequency currents produce the increase in temperature in passing at the point where they are measured, which is a well understood physical principle. Conductivity from the surface does not affect these values, and the temperature begins to fall as soon as the current ceases to flow. For cautery, the heat has to be conducted down from above and requires from two to three minutes to penetrate to distances of the order of those in Table VI. The cautery analogue for the last line in Table VI is 2.5 degrees rise in two and one-half minutes but 0 degree at the end of the eight-second application and for the first one and one-half minutes thereafter.

The heat produced in tissue by the passage of an electric current (direct or alternating at any frequency) is proportional to the square of the amount of current passing through the tissue. Thus the heating effect on a given sample of tissue of a certain current value is the same regardless of the type of oscillator from which the current was derived. The current from a simple tube oscillator has good cutting qualities, but is more likely to be followed by bleeding than in cases where current from the multiple spark gap type of oscillator is used. Referring to Figure 3-*a*, which represents the voltage curve for current from the vacuum tube type, we see that the current would consist of a succession of short bursts in alternating directions. Each half cycle reaches such an amplitude as is necessary to cause sparking at the cutting electrode. Thus, there are 2,500,000 current impulses of sufficient intensity to cut each second where the current has the usual frequency of 1,250,000 cycles per second. It will be noted that the curve is quite steep between the peaks, so that there is very little current between these cutting impulses. The damped wave train, as from the spark-gap type oscillator (Fig. 3-*b*) has certain cycles of less intensity than that required for cutting. Thus, for the same cutting qualities the tube oscillator will operate on a smaller current value than the spark-gap type will. Or, saying the same thing in another way, the tube type current will cut faster than the spark-gap type with the same current value. This slowed cutting with the larger cur-

rent value gives the spark-gap type current the coagulating qualities that prevent bleeding by virtue of the greater heat produced by the larger amperage of the cutting current. The tube current could be easily increased to this value, but as each impulse would then have a more intense sparking value, unwanted sparking occurs. In using the tube machine, therefore, the cutting is generally effected with current suitable for that purpose, and then hemostasis is effected by a current whose peak voltage is less than the sparking value, and which, consequently, will not cut.

Thus each type of machine has advantages over the other. The tube machine effects cutting at a lower current value and consequently produces less heating at depths in tissue, while the spark-gap type employs more current for the same cutting and gains hemostasis with the increased heat near the cutting electrode. In the preceding tables the type of current was not stated, since this would have no meaning in view of the actual milliameter readings. Well known electrosurgical units of both types were employed.

Ward[18] points out that electrosurgery is dangerous in the hands of novices and others who do not understand its possibilities. He also points out that wounds made by cutting current cannot heal by primary union because about two millimeters of tissue on each side of the cut may be killed. According to this author, malignancies may be killed with ease to a depth of 1.5 cm. by these currents. For such uses it is highly recommended. Cutting, with a minimum of damage to tissue, is effected by moving the cutting electrode at a maximum speed and with the smallest usable current value. The cutting electrode should be a wire small enough just to stand the mechanical strain. Such cutting, especially when a minimum value of uniformly oscillating current is employed, leads to bleeding. Bleeding may be stopped without doing a large amount of additional damage because of the lower current value employed. If, for instance, coagulating requires one-third the current employed in cutting, the heating effect in tissues would be one-ninth that of cutting, granted that both are done with the same speed. The coagulating electrode probably would necessarily move more slowly than in the above described procedure, but still it would seem less harmful than the cutting operation.

The question of frequency of oscillations of the currents applied to tissues deserves more mention. Schereschewsky[11] studied the

effects of high frequency oscillations on tumors implanted on rats and chickens and found that the currents studied (frequencies between 8,300,000 and 135,000,000) would all kill the growths, but that the intermediate frequencies were the most deadly. In his work, the region to be treated was not used as a conductor in the circuit, but as a dielectric between insulated plates which were connected to the oscillator. Calculations by Lamb[6] fully explain this differential action of the various frequencies on tissues. Applying his formulæ, we find that frequencies that would mechanically destroy the smaller cells by vibration range around 100,000,000 cycles per second; and, for the larger cells, about 20,000,000 cycles. The smallest cells that might be mechanically destroyed by a frequency of 1,250,000 cycles per second (as in electrosurgical units) would be over 700 microns in diameter. Since cells of that order of magnitude are not encountered, the frequency seems to be well chosen from this standpoint.

EXPERIMENTS ON ANIMALS

In this series of experiments many questions presented themselves for investigation. Among those studied were the heating of tissue at depths by cutting and coagulating currents, from which the rate of blood flow was calculated, streamlines of current through the body of living animals and the relative amount of heating in the organs and the blood stream. When a cutting electrode or an electrode of similar size was employed, samples of tissue were taken at the burned region for microscopic examination. The findings from this study will be reported in another section of the paper.

The operations on dogs were sterile and the dogs were allowed to live varying periods of time after the burning before the autopsies were performed in order to be able to observe secondary effects.

The technic employed here was similar to that already described. The anesthetized animal was placed on his back with a plate electrode applied to some portion of his back from which the hair had been removed. In cases in which the heating effect of cutting currents near the actual point of cutting were to be studied, incisions were made and thermocouples which were incased in bakelite needles were inserted at appropriate positions in the organs.

TABLE VII. TEMPERATURES PRODUCED IN THE DOG'S PROSTATE AND RECTUM

S_1	S_2	Temperature Change	Time Seconds	I	L	Notes
77.4	77.7	0.06°C	3	500	1	Thermocouple No. 1 in rectum, no fecal matter; No. 2 in prostate 0.5 cm. from point of application of loop.
77.0	77.2	0.04	3	500	1	
78.0	140.	12.98	3	480	2	
85.0	148.	13.19	3	480	2	S_1 return to 85 in 2 minutes, water running at room temperature.
79.0	134.	11.51	3	480	2	
79.0	131.	10.88	3	480	2	Temperature return to normal in 2 minutes, water running.
81.5	128.	9.74	3	480	2	
76.5	109.	6.80	3	480	2	S_2 return to 80 in 4 minutes, water not running.
74.0	106.	6.70	3	480	2	

TABLE VIII. TEMPERATURES PRODUCED IN PROSTATE

Temperature rise C (average)	Current	Time of application Seconds	Conditions
12.0°C	500	3	1.8 cm. from application of current—no water flow.
7.1	500	3	1.8 cm. from application—water flowing —prostate in puddle.
18.9	1230	3	0.8 cm. from button electrode, area 63.7 sq. mm., no water.
2.2	375	3	0.8 cm. from cutting loop—water flowing.
6.1	375	3	0.5 cm. from cutting loop—water flowing.

The results of the studies of the heating effects in the prostate are best shown by a few typical tables of data. Table VII is copied from the laboratory notebook complete. S_1 and S_2 are instrument readings before and after the three-second applications of current. The difference between these two readings multiplied by .2095 gives the temperature rise during the interval, recorded in the third column. I is the current value employed in milliamperes, and

L shows the location of the thermocouple. The progressively smaller temperatures produced at the point where the thermocouple was located change in the path of current flow due to changes in the tissue. The temperatures in the rectum will be referred to later.

Table VIII shows the results of using currents that are of such densities as barely to cut in the first two lines, and of coagulating density in the last two lines. The current density in the case where the button electrode was used (third line) was 19.3 milliamperes

TABLE IX. CUTTING CURRENTS ON TESTICLE

Temperature rise° C	Current value	Distance	Time Seconds	Note
5.87	300 M. A.	1.5 cm.	3	
13.85	300	1.0	3	Testicle in scrotum, animal alive, water running copiously.
22.38	500	1.0	3	
24.88	500	0.9	3	
17.30	375	0.9	3	
27.29	500	0.8	3	
45.80	500	0.6	3	Intervals between current applications 10 seconds.
27.89	250	0.4	3	
35.80	250	0.3	3	

per square millimeter of surface, at the surface of the electrode. The current values generally used are about double the value for which the data in the last line were taken. Doubling this value gives a temperature rise of approximately 24.4 degrees centigrade, at 0.5 cm. from the active electrode.

Tables VIII and IX enable one to deduce empirical relations between heating, current and distance for constant periods of application of current. It will be seen that the approximate law already given seems to hold roughly. The spreading of the streamlines of current is not quite normal in the data on testicles because of inadequate space. For an organ surrounded by tissues and body fluids the heating would be much less.

Results for the cautery analogue to Tables VIII and IX are not given because here, again, there was no temperature rise for immediate readings. For distances comparable to those in Table VIII the temperature rise, which is due to heat conduction, is detected in about thirty seconds and reaches a maximum in about fifty seconds. For example, a four-second application of the hot blade to a prostate gave a temperature rise of 0.25 degrees centigrade in fifty seconds at a point 0.8 centimeters deep. For a clearer explanation of the temperature changes involved the small curve inset

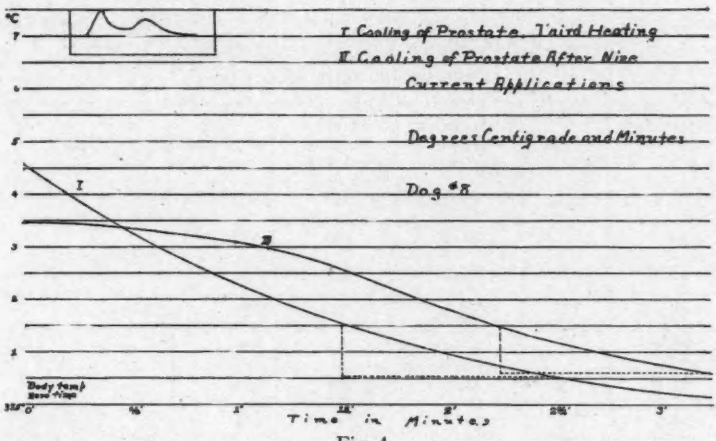

Fig. 4

in Figure 4 is presented. This represents the general shape of the temperature curve for a point about 4 millimeters below the surface of an organ through which current is passed for a short interval. The steep part represents the actual heating, current being switched off at the peak. From the peak begins the cooling curve, which assumes the usual logarithmic form for an interval of about thirty seconds, after which it becomes level and finally begins to climb again. This is due to the fact that a wave of conducted heat has arrived at that point from the hotter tissue above, the spread being faster than the rate of cooling. After this secondary rise the cooling curve becomes about normal again. For greater distances this secondary hump in the cooling curve becomes

less noticeable, or is absent, because of the dissipation of heat during the time required for conduction. This secondary effect represents the complete curve for the application of cautery, which accounts for the fact that the immediate readings in the above mentioned cases were zero. In tissue well vascularized, it seems certain that tissue less than two millimeters below a surface which is cut by a cautery blade is unlikely to be damaged.

Table X shows temperature values obtained by applying current to the prostate of a living dog in a sequence. Water at room

TABLE X. TEMPERATURES IN THE PROSTATE OF LIVE DOG PRODUCED BY APPLYING CUTTING CURRENT IN SEQUENCE WITH ELECTRODE (4 mm. diameter)

Temperature before application	Time Seconds	Temperature after application	Interval between applications	Current value	Note
38.0°C	3	48.2°C	20	500 M. A.	
40.3	3	57.0	20	500	
46.1	3	53.2	20	500	Readings taken with thermocouple 1.8 cm. from active electrode. Prostate bathed in water.
46.6	3	50.8	20	500	
47.7	3	55.0	20	500	
47.9	3	54.1	20	500	
46.7	3	52.6	20	500	

temperature was allowed to flow on the point of application so that the most heated point was subjected to the greatest cooling effects. There were twenty-second cooling periods between each application. The column of temperatures immediately before each application represents temperatures only a little higher than that for the whole prostate, and the column of temperature values immediately following the current application are true only for the particular point at which they were taken: at a depth of 1.8 centimeters.

An interesting point is quite clearly shown in the fact that the temperatures recorded reached a maximum which was not attained in subsequent applications of current. Figure 5 shows essentially

the same effect.† For a steady current flow the heating of a conductor is a function of K $(1-e^{-mt})$, which simply shows that for large values of the time element, *t*, the temperature reaches a constant value at which heating and dissipation of heat are at equilibrium. Here, however, the temperature actually overshoots this constant value which is finally attained because blood flow is probably stimulated in the undamaged tissues nearby, thus increasing the rate of dissipation from that source. This is not to be confused with another effect of the flow of blood which will be mentioned later.

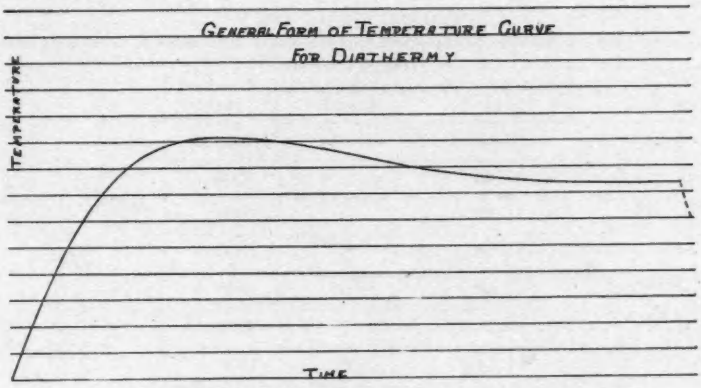

Fig. 5

Table XI shows that currents of mild coagulating density heat underlying tissue to a maximum temperature, after which the temperature drops to a constant value in about nine or ten seconds. The current density at the electrode was 10.2 milliamperes per square millimeter at the surface of the electrode, and the temperatur measurements are for a centimeter below. Current of such density, and so applied, blisters skin and coagulates tissue for a few millimeters below, as has been stated earlier in this paper. The first three lines in Table XI show an effect that was studied at some length. These increased heatings for the same conditions

†Though this effect was observed many times in the present work, this particular curve was copied from Hemingway and Hansen: Temperature Distribution in Local Therapy Treatments. *Radiology*, 17:1258.

may be due to the stopping or restricting of blood flow in the tissue that undergoes some degree of coagulation, thus raising the maximum attainable temperature to a higher value than it would be if the tissue could remain normal.

This decrease in blood flow due to coagulation in the vicinity of the point at which the temperature is measured was calculated by a method which is independent of any stimulation of flow in the undamaged tissues near by. In Figure 6, curve I gives data

TABLE XI. TEMPERATURES IN RABBIT LEG MUSCLE PRODUCED BY APPLYING CURRENT FROM A BUTTON ELECTRODE

(Area .97 sq. cm.)

Temperature rise	Time of current application Seconds	Current value
9.86°C	3	1000 M. A.
10.46	3	1000
11.32	3	1000
14.69	6	1000
14.48	9	1000
7.26	2	1000
11.44	4	1000

Cooling time between applications being allowed.
Measurements taken 1 cm. from active electrode.

for the cooling of a dog's prostate in approximately its normal position with normal blood flow. Curve II gives the rate of cooling of the same point under the same conditions after five applications of current, three seconds' duration, and a current value between 500 and 600 millamperes. The point at which the temperature was measured was 0.8 centimeter inside a lobe to which current was applied from a sphere 4 millimeters in diameter. Curve III shows the cooling rate under the same conditions except for the fact that the urethra was tied tightly on each side of the prostate so that there was no blood flow. Using the cooling rate without blood flow as a correction, the rate of cooling due to blood flow was deduced and the consequent rate of blood flow for curves

I and II calculated. The normal rate was found to be 0.68 grams of blood through a cubic centimeter of tissue per minute. After the burning, data taken from curve II, the rate of flow was 0.11 grams per c.c. of tissue per minute. This latter value, of course, represents an average throughout a mass of tissue through which the amount of flow was not uniform.‡

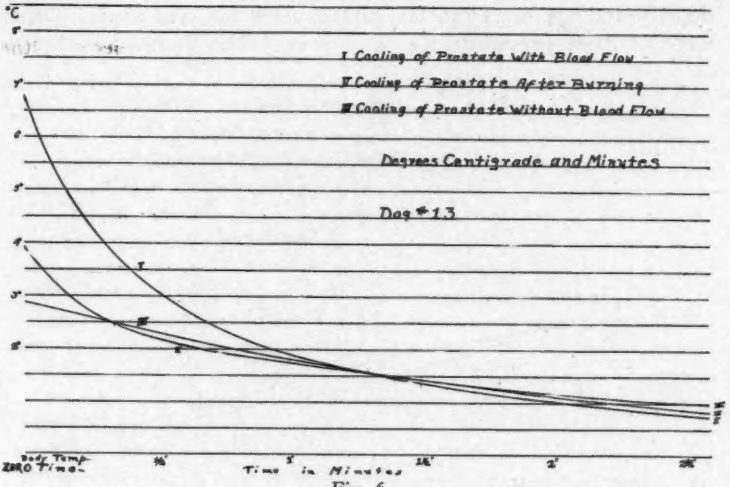
I Cooling of Prostate With Blood Flow
II Cooling of Prostate After Burning
III Cooling of Prostate Without Blood Flow
Degrees Centigrade and Minutes
Dog #13
Time in Minutes

Fig. 6

Taking data from Figure 4 as indicated by the dotted lines, we find for curve I a rate of 0.45 grams of blood through a cubic centimeter of tissue per minute; and for curve II, 0.31 grams per cubic centimeter per minute. Curve I was taken following three applications of current of coagulating density from a button electrode. Curve II was taken following three additional applications of the same nature and two applications from a smaller electrode with the current proportionately reduced to preserve the same approximate current density. The time of application was three seconds with cooling time allowed between.

‡The heat loss per minute due to blood flow was equated to the heat convected away by blood. $M \times S \times T$ (for blood) = $M \times S \times T$ (for tissue) the mass of blood being the unknown in the equation, where M is mass in grams, S is the specific heat of the substance, T is the temperature change involved for the substance in the interval. The specific heat of blood was assumed to be 0.97; the specific heat of prostate, 0.83; the density of prostate was 1.05 gms. per c.c.

In Figure 7, curve I was taken following eight applications of current. The periods of application were three seconds, and cooling time was allowed between applications, the rate of cooling being taken following the eighth heating. The current value was 500 milliamperes, applied from a small coagulating ball. Curve II was taken following the nineteenth application. Three applications preceding the data for the latter curve were at coagulating current density and applied from the surface of a ten cent piece. Others were as those preceding the first curve. The thermocouple junc-

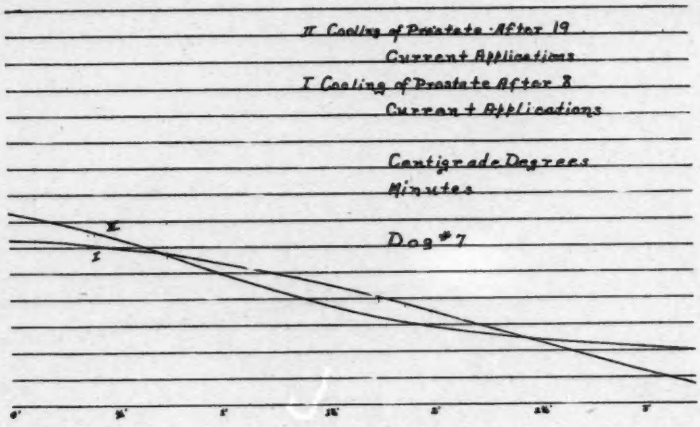

Fig. 7

tion was 1.8 centimeters deep in the prostate. The first curve indicates a flow of blood equal to 1.0 gram per cubic centimeter of tissue per minute. The second assumes the approximate slope indicated by no blood flow after passing the secondary "hump" in the cooling curve.

In order to determine the heating effects of cutting currents in the human prostate during operation, data were taken from a number of prostatic resections and from a small series of suprapubic cystotomies, preliminary to prostatectomy. The method of placing the thermocouple in the prostate for the transurethral resections was similar to that employed in implanting radon seed into the gland. Special trocars with an inside diameter of a millimeter and a half were inserted through the perineum into the prostate under

TABLE XII. TEMPERATURES PRODUCED IN A TRANSURETHRAL PROSTATIC RESECTION EMPLOYING HIGH FREQUENCY CURRENTS

Temperature before cut	Temperature immediately after stroke	Duration cutting stroke Seconds	Current value	Notes
37.6°C	40.4°C	5	900 M. A.	
37.70	40.53	8	800	4 minute pause.
37.73	41.37	6	700	
37.70	40.08	12	700	Cutting high.
38.01	41.37	7	800	
38.60	42.13	9	700	
38.64	41.08	8	800	
38.70	40.57	10	800	
38.70	40.58	8	800	
38.60	41.78	8	800	
38.30	41.06	8	750	
38.31	41.08	7	850	On lateral lobes.
38.37	39.88	9	800	
38.31	65.73	5	800	Cutting near median portion.
38.32	40.34	7	850	
38.14	41.88	6	900	Laterals again.
38.14	51.23	7	850	Median incision.

the guidance of a rectal finger. The obturator was removed and the thermocouple inserted through the lumen, the trocar was gradually removed and the bakelite needle containing the thermocouple allowed to remain embedded in the prostate. In the open suprapubic operations the internal orifice of the bladder was exposed and the trocar inserted under the guidance of the eye, at a definite distance from the projecting surface of the lobe which was to be burned.

Tables XII, XIII and XV are typical examples of the heating effects obtained with these procedures. Table XII represents a

TABLE XIII. TEMPERATURES PRODUCED IN A HUMAN PROSTATE BY APPLYING CUTTING CURRENTS FROM A 4 MM. COAGULATING BALL IN AN OPERATION PRELIMINARY TO PROSTATECTOMY

Temperature before application	Temperature immediately after application	Duration of application Seconds	Current applied	Notes
37.40°C	46.02°C	2	700	Water running, suction functioning.
38.00	45.26	2	700	Thermocouple approx. 2 cm. from point of application of current.
38.72	47.25	2	700	
38.96	49.20	3	700	
38.96	46.56	3	600	Interval between applications about 2 minutes except in two cases where it was longer.
39.20	45.74	4	500	
38.28	45.90	3	600	
38.36	47.55	4	500	
38.54	49.66	6	500	
37.4	42.1	1	1100	In rectum.
42.1	43.2	1	1100	In rectum.
39.3	63.0	1.5	1100	In prostate 1 cm. from application.
40.2	51.9	1	700	
41.7	41.9	?	700	
41.3	50.5	?	700	

single operation on large bilateral lobes with varying current values, as well as the duration of cutting strokes. There were seventeen readings made during the operation which required fifty-five minutes. It is to be noticed that with the thermocouple located as it was, near the median portion of the prostate, temperature readings were not high while the cutting was being performed high up on the lateral lobes, but as the loop approached the median portion the temperature suddenly rose to 65.73 degrees centigrade, as seen in the fourth to the last lines, cooled back to 38.32 degrees during a rest period, and when the resection was performed again near

the median portion of the prostate, one seven-second stroke 850 millamperes, produced a temperature of 51.23 degrees.

It is fair to assume that similar temperatures were created throughout the circumference of the orifice at points equally distant from the site of current application, certainly sufficiently high to exert destructive influences upon the tissue so affected, as these recorded temperatures are well above the thermal death point.

TABLE XIV. TEMPERATURES IN THE HUMAN PROSTATE PRODUCED IN A TRANSURETHRAL OPERATION EMPLOYING THE THERMAL "PUNCH"

Temperature before cut	Temperature after cut	Time employed	Notes
37.50°C	37.50°C	3	
37.59	37.59	3	Two minutes between cuts.
37.83	37.83	2.5	

Four other cuts were made in this operation, but data could not be obtained. Data below are for a different case.

37.62	37.62	3	Temperature in ½ minute, 39.06; in 1 minute, 37.98.
37.62	38.22	3	
37.87	37.87	4.5	Temperature in ½ minute, 38.26.
39.06	39.06	4	Maximum reached, 39.18.

Table XIII presents records of temperatures obtained in an open suprapubic operation with the electrode definitely placed at 2 centimeters away from the site of burning, in the upper table, and 1 centimeter in the lower. In the upper table, with the prostate bathed in water and with very short current applications, an average temperature rise of about 9 degrees centigrade is recorded. In the lower table, with higher current values but with shorter applications, there is recorded a temperature increase of 26 degrees centigrade above normal; 5.8 degrees was recorded by a thermocouple in the rectum. It is interesting to note that the rate of cooling in the rectum is decidedly slower than in the prostate.

Table XIV gives temperature records in two cautery punch operations for median bar removals. In the first instance it is

TABLE XV. TEMPERATURES PRODUCED IN TRANSURETHRAL PROSTATIC RESECTION BY HIGH FREQUENCY CURRENTS

	Temperature change produced by stroke	Time of stroke Seconds	Current employed	Location of thermocouple and notes
1.	2.65°C	10	575 M. A.	In prostate above cutting.
	1.70	5	600	In prostate above cutting.
	7.72	9	575	In rectum as near as possible to prostate.
	7.08	7.5	610	In rectum as near as possible to prostate.
	8.31	7.5	610	In rectum as near as possible to prostate.
2.	0.36	8	550	In prostate above cutting.
	1.51	40 sec. after above stroke by conduction		
	0.63	4	200 (coagulating)	In prostate above cutting.
	3.40	40 sec. after above application by conduction.		
	1.14	5	575	In rectum.
	1.25	7	575	In rectum.
3.	3.44	5	650	In med. lobe, cutting at 4 o'clock.
	2.58	2	200 (coagulating)	In med. lobe, coagulating at 4 o'clock.
	10.30	7	600	In med. lobe, cutting at 6 o'clock.
	1.20	9	600	In lat. lobe, cutting at 3 o'clock.

Instrument went off scale in a subsequent cut which removed tissue from thermocouple tip. This indicated a temperature rise of more than 40.2°C.

to be observed there was no temperature elevation at the time of cutting strokes and but a very small accumulative rise during the sequence. In the second operation the same thing is to be observed, except in this instance there was more accumulative heat rise, but at most amounted to only about one degree and a half. Within thirty seconds after the initial excision the temperature at the thermocouple reached a maximum of 39.06 degrees, but at the

end of a minute it had cooled to 37.98 degrees due to heat conduction.

The first part of Table XV shows principally temperatures produced in the rectum of the patient by high frequency currents. Here the temperatures range from 7 to 8 degrees above normal,

TABLE XVI. TEMPERATURES PRODUCED IN TRANSURETHRAL PROSTATIC RESECTION BY HIGH FREQUENCY CURRENTS

Temperature change during stroke	Duration stroke Seconds	Current	Notes
4.20°C	6	800 M. A.	On lateral lobe.
4.02	5	800	On lateral lobe.
1.65	4	800	On lateral lobe.
7.50	7	800	On median portion.
8.26	8	800	On median portion.
11.85	6	800	Lower lateral near median.
1.35	10	400	Coagulating.
0.35	6	350	Coagulating.
6.76	5	700	Cutting current for bleeding.
1.35	6	700	High on lateral.
1.35	6	700	High on lateral.
4.35	8	650	Lower lateral.
12.44	7	700	Median.

Between strokes temperature fell to within .75° of normal.
Operation lasted approximately 40 minutes.

which is exceptionally high for the cases in which rectal temperatures were observed.

The second part of the table was for a case in which the thermocouple was not placed in the direct line of current flow, but above it. Here it will be noted that the immediate temperature rise, due to current passage, was smaller than the rise due to heat conduction; for example, the temperature rise for one stroke was 0.36 degree centigrade, for the immediate current passage, and 1.51 de-

grees centigrade by conduction after forty seconds. We also observe a second rise of almost three degrees by conduction, which shows that high temperatures were produced nearby.

The third part of the table shows results similar to those in Table XII where the cutting was in the lobe in which the thermocouple was inserted. The temperature rise was large and in this instance recorded 10.30 degrees centigrade.

In most of the experiments on dogs and in six of the human operations thermocouples were placed in the rectum. This led to some surprising findings. When current was applied in the prostate, the temperature rose quite high in the rectum in some cases, and was negligible in others. It was immediately surmised that the explanation probably lay in the difference in the amount and in the nature of the rectal contents. Two factors in the amount of heating would be the nearness of the prostate to the rectum, and the conductivity of the matter within. In one human operation the temperature was observed to rise 8 degrees centigrade during one cut in the prostate, though the temperature in the perineum was little affected. Here evidently the materials in the rectum were much better conductors than the muscular and fatty tissues nearby. The fact that the indifferent electrode was placed low under the buttocks was probably also a factor in concentrating the current. In the other human cases the temperature changes in the rectum were generally less than a degree. The same effect was observed in dogs, and in one case a maximum temperature of 16.8 degrees above normal was recorded, the thermocouple lying directly under the prostate in the rectum. In all other cases the temperature changes were generally from 0.1 to 2 degrees, except when large currents were applied from plates, as in diathermy.

These findings led to an investigation of current paths in a limited way in connection with the main problem. It was suggested that diseased tissue might be a better conductor than normal tissue, due to the fluids and autolyzed materials. This was tested in two dogs by observing the heating in the rectum under a particular set of conditions at the beginning of the experiment, then continuing to note temperature effects at intervals throughout the experiment after the walls of the rectum had been crushed by gripping them several times with a heavy forceps. In both cases the injured portion heated more after having been crushed than

before, provided as much as a half hour had elapsed after the crushing. This effect progressed with time throughout the experiments, and in one case it became considerable, definitely passing the thermal death point of tissues, the current employed being unusually large. However, here the high temperatures ranged between 8 and 12 degrees for diathermy currents (1230 milliam-

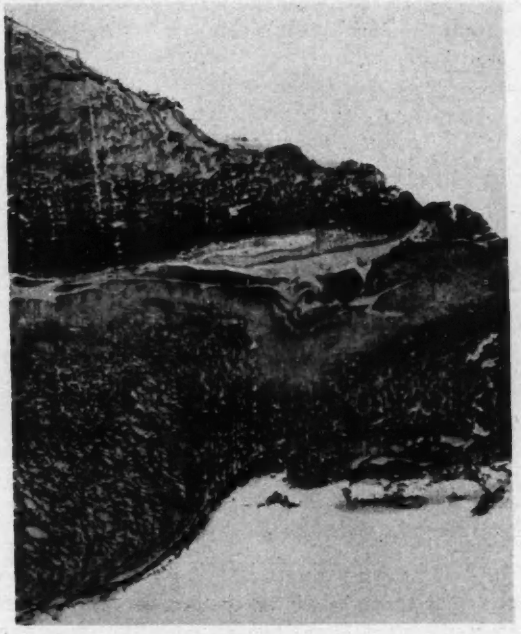

Fig. 8. Dog No. 1.

peres) applied between plates, one of which was placed on the shoulders and the other very near the anus. This suggests the wisdom of careful observation of the rectum before high frequency prostatic resections. It seems evident that the presence of constipated fecal matter in the bowel, ulcerated mucosa with exudate, or infected hemorrhoids, might serve to concentrate the current, and in extreme conditions do damage. This may explain some of the

unfortunate recto-urethral fistulæ which have been reported following some of these operations.

In subsequent experiments on dogs and rabbits diathermy currents were caused to flow through the bodies of the animals as in the case mentioned above, and the temperature changes in several organs noted. It was found that where the blood supply was best the temperature change was most profound. The alimentary canal changed slightly less than the large blood vessels, and muscle tissue was found to heat very much less. The spinal canal was

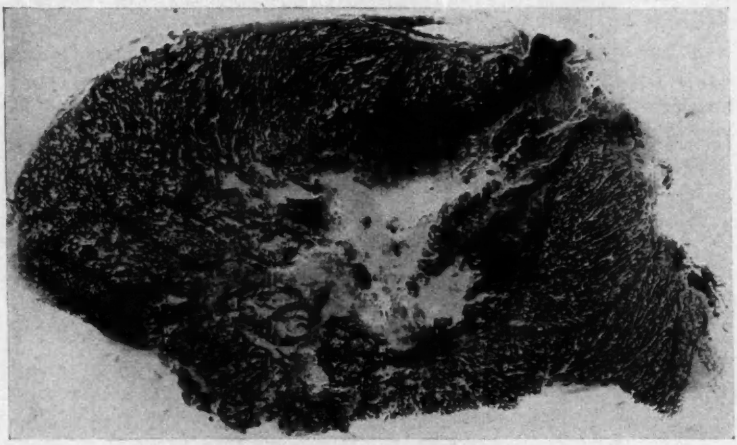

Fig. 9. Dog No. 4.

found to heat in amount comparable to that in a blood vessel. This suggests that there might be danger in applying strong diathermy currents between plates placed along the spine over considerable periods. The fact that the spinal canal has none of the high resistance membranes to act as current diverters and that it is a fair electrolyte with little circulation would seem to be a caution against such practice. This caution would also apply to the use of cutting currents in this manner.

PATHOLOGY

The pathology changes occurring in the prostate following the application of high frequency currents have been studied on twenty

dogs, and three human subjects. The prostates have been subjected to different temperatures and varying durations of application, and have been studied at different time intervals following the applications.

Four dogs died of sepsis, at intervals ranging from one to three days following the current applications. The prostates of three of these animals were so completely destroyed by necrosis that no prostatic tissue was left for pathologic study.

I am indebted to Dr. Cowdry, Professor of Cytology at Washington University, and to Dr. George Ives, for their valuable assistance in the study of the pathology specimens. Only a few of the representative specimens will be detailed since the pathologic changes, both immediate and late, have so closely corresponded in all the specimens.

Dog No. 1 lived fifteen days after the prostate was burned at its internal orifice by five applications of current, 600 milliamperes, with two-second applications, following suprapubic exposure. The pathologic specimen demonstrated coagulation necrosis at the site of burn in which nuclear structure was no longer visible. There were only a few places in the gland where the epithelium was normal. Throughout the gland the acini were plugged with pus. There was a diffuse inflammatory change with leukocytes and lymphocytes through the organ and hemorrhagic changes in many of the acini. The interacinar tissue was very edematous and heavily infiltrated with polymorphonuclear leukocytes.

A noticeable change consisted of a marked peri-urethral infiltration, the wall of the urethra being edematous and heavily infiltrated with polymorphonuclear leukocytes. This zone completely encircled the canal.

The whole process represents a diffuse septic change throughout the substance of the gland.

Dog No. 4.—Suprapubic exposure of the prostate was made. The bladder was not opened, the surface of the prostate being treated with ten high frequency applications, three seconds each, ranging from 300 to 600 millamperes. The dog died in twenty-four hours. Microscopic section showed a dense zone of coagulation necrosis near the surface, the area extending deeply into the tissue, in the central part of which all chromatin had left the nuclei

of the cells. Cell outlines were fairly distinct. The cells and tissues between them were strongly acidophilic. In this area there were but few nuclei containing chromatin and these were either polymorphonuclear cells or macrophages. Below this zone there was noticed marked hemorrhage which entirely surrounded the injured area. In this limiting zone of hemorrhage there were cells which did contain distinct nuclei, but these nuclei were pycnotic and the cells tended to be separated. The cytoplasm showed vacuolization and fragmentation. Further on was an area in which the

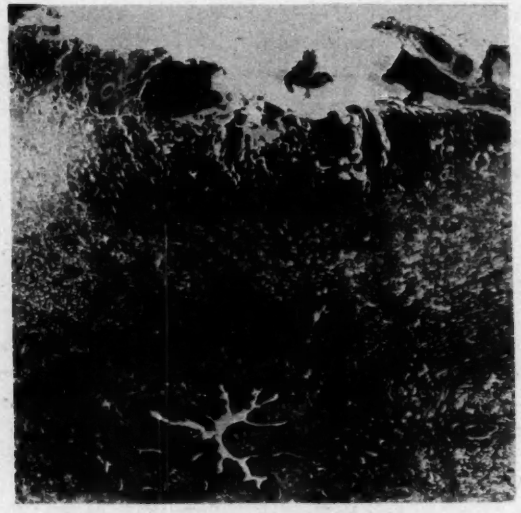

Fig. 10. Dog No. 8.

nuclei were not pycnotic, but appeared more or less normal. The outlines of the acini were quite distinct though there was some desquamation of the cells into the lumina and frequent evidence of cellular shrinkage. In this relatively normal tissue which encircled the burn there were no signs of hemorrhage. A striking observation was the presence of areas of necrosis completely surrounding the urethra even on the side distal to the burn, resulting in all probability from the tendency of the currents to follow the paths of electrolytic fluids. There were thus observed three zones:

first, coagulating necrosis; second, fragmentation and hemorrhage; third, relatively normal zone with evidences of fluid change in the tissue.

Dog No. 8.—Suprapubic exposure of the prostate was made using seven current applications with a large electrode (size of a one cent piece), 1230 milliamperes, three-second applications on the lateral surface of the prostate. Microscopic section showed a

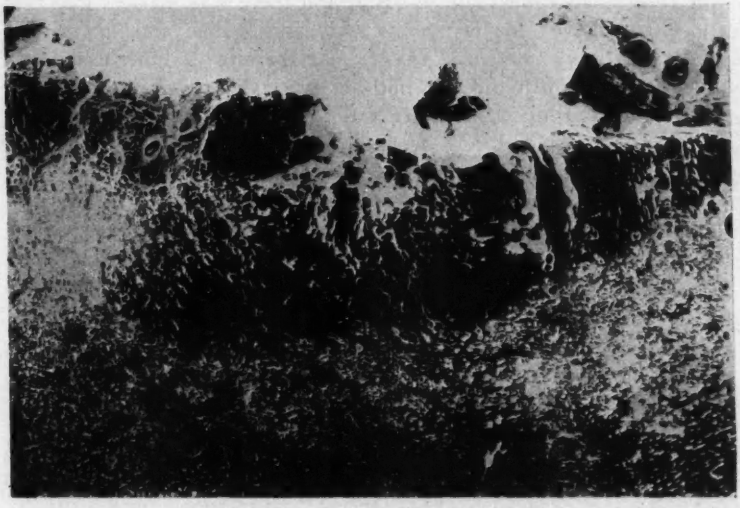

Fig. 11. Dog No. 13.

burned area covering a large surface. The coagulation necrosis did not penetrate deeply. There were many hyaline changes in the tissue adjoining the necrotic zone and the nuclei had lost their affinity for basic stains. Hemorrhage was very slight, and there was marked pycnosis of the nuclei of the epithelial cells and desquamation into the lumen. The outlines of the acini were quite distinct. The urethral epithelium was broken down and had mostly disappeared. This specimen also showed a tendency for destruction at the urethra well away from the burn with normal tissue intervening. It is to be noted in this specimen that the heat pen-

etration from the surface with a broad diathermizing electrode was not as pronounced as in dog No. 4.

Dog No. 13.—This proved to be a fatal experiment. Suprapubic exposure of the prostate was made, with seventeen two-second applications, 500 to 600 milliamperes, to the surface of the gland. Autopsy was done immediately. The surface was much disintegrated beneath the zone of coagulation. There were areas which seemed mostly hyalin where the acini could not be recognized. The cells had a faintly bluish color, and there was marked pycnosis and shrinkage of nuclei over a wide area which was not visible in the relatively uninjured tissue. At the site of burn extending toward the urethra the cell outlines were destroyed in areas but were not uniformly so. There was much hemorrhage and exudation. The red blood cells were largely destroyed, and looked as though there had been areas of hemolysis. Leukocytic response was but slight, and there was a great deal of desquamation into the lumen of the acini. This condition extended around the urethra but not into the acini of the other side. The epithelial cells of the urethra stained poorly and were greatly destroyed. There was great engorgement of the vessels immediately beneath the epithelium of the urethra.

There were seven other specimens of the dogs' prostates which were studied, but since they coincided exactly with these above described they need no detailed description.

Several dogs' testicles were subjected to high frequency applications. The current was given from ten to seventeen times on each organ for two seconds application with 500 to 600 milliamperes. The heat records are given above and show uniformly higher temperatures than the prostate. Pathologic specimens showed the same zone of coagulation necrosis as observed in the prostate, but the other zones were not distinct. The whole organ was involved in a generalized hyalinization and normal structures were absent in all portions of the gonads in dogs which lived over two days.

SPECIMENS FROM HUMAN PROSTATES

Specimen No. 1.—Specimen was removed nineteen days after suprapubic cystotomy, at which time nine current applications, two seconds each, 500 to 700 milliamperes, were applied to the top of

the middle lobe. Maximum heat generated at 2 centimeters away from the site of the burn was 49.6 degrees centigrade. Specimen removed contained tissue 1 centimeter deep. Specimen showed grossly an area of yellowish brown necrosis at the previous site of burn. On section the gross specimen showed microscopic changes apparently 0.5 centimeter deep in the tissue. Microscopically throughout the whole specimen the acini showed marked desquamation of epithelium, and epithelial linings had degenerated and in places completely broken up. The interstitial tissue contained a considerable accumulation of fluid, failed to color with eosin in the usual way and was infiltrated with lymphocytes and leukocytes. There was practically no hemorrhage in the tissue.

The persistence of the necrotic ulcerated area nearly three weeks after the burning with an ordinary electrode loop gives evidence of the severe reaction and the persistence of the process. The tissue throughout possessed no evidence of normal structure.

Specimen No. 2 (Schroff).—This specimen of a human prostate was removed at a two-stage operation. A part of the median lobe immediately was heated to 65 degrees centigrade for two minutes and was checked against an unheated control specimen. The heated tissue appeared grossly pale and lost its glistening appearance. It was definitely different in gross appearance from the control specimen and yet microscopically there was practically no difference in the two specimens. In other words, the effect of this heat applied for a short time, even at this rather high temperature, had not manifested itself histologically in cell change. Some of these cells, if allowed to remain in the body following the heat application, would have later shown degenerative reactions.

The pathologic changes observed following high frequency applications exhibit three distinct zones of damaged tissue:

1. Zone of coagulation and complete cell destruction.

2. Zone of fragmentation, hemorrhage, cell shrinkage and pronounced nuclear changes.

3. Relatively normal zone which is the most variable of the three, and depends chiefly upon the time element. Specimens taken immediately, or shortly after high frequency applications, may exhibit no demonstrable histologic evidence of cell change in this zone, but after a few days may reveal definite necrosis.

These findings coincide exactly with those observed by Kukens[5] and Magyary.[7] The complete histologic effects of the electric current on tissue can be accurately observed only through animal experimentation, since daily observation is required to determine them. Immediate observation does not show all of the damage that is done and later studies, as are compatible with proper surgery, will show either diffuse disseminated lesions or evidences of repair.

That tissue is killed by cuts with high frequency instruments is well demonstrated by the fact that healing is slower and and infection more likely. This has been admirably shown by the work of Gottesman, Perla and Zeigler.[3] These authors showed that the time of healing was three times as long as with the knife cuttings, and that the scar and slough were worse. These authors furthermore state "that the incisions with an electric current are unsound and unphysiological, because they add more necrosis to the burden of repair."

Ellis,[1] comparing wound healing of electrosurgical wounds to knife wounds, showed in 120 dogs that only 60 per cent of the electrosurgical wounds seemed to approximate by primary intention as compared to 97.5 per cent for knife wounds. These 60 per cent of apparently healed wounds were considerably weaker than the knife wounds after twenty-one days of recovery as tested by applying known forces and noting the force required to pull tissue apart.

Magyary,[6] using guinea pigs, made a comparative study of the surgical knife and electrical high frequency incisions, with reference to wound healing following the spraying of the wounds, after they had been closed, with cultures of various bacteria. In every instance the wounds produced by the surgical knife healed more quickly and with less reaction than the others.

CONCLUSIONS

The interpretation of the foregoing from the standpoint of the clinician is quite clear. In using the various high frequency cutting instruments, tissue damage is often produced more deeply than is generally desirable, and often to some extent is unavoidable. High current densities applied for more than a second may do damage at depths from a few millimeters to over a centimeter.

In order that tissue may be cut with high frequency currents, an intense heat is required at the active electrode. To produce this heat it is necessary for the current to pass through the tissue from an indifferent electrode and focalize at this point. In so doing, the paths of current, in their concentration toward the active electrode, generate varying degrees of temperature deep within the tissue, away from the point of active burning; whereas in removal with the actual cautery, approximately the same temperature is applied at the surface of the cut, but no heat is produced within the tissue, except by conduction from the surface.

The analysis of our experiments with the high frequency currents shows conclusively that, at depths within the tissue of at least 1 centimeter away from the active point of burning, temperature changes well beyond the thermal death point of tissue have been produced; whereas with the actual cautery, the heat registrations less than a half centimeter away, after repeated applications at the same site, have been negligible. The temperature which causes thermal death to tissue cells certainly lies between 44 and 52 degrees centigrade,[9] probably about 47. The heart stops beating in cats,[9] dogs[4] and mice[12] at a temperature of from 44 to 45 degrees. Chick cell cultures[10] cease to grow and finally die after a few days of exposure to 44 degrees centigrade; at 47 they die in one and a half hours; and die immediately on reaching temperatures around 50 degrees.

An analysis of the specimens removed with high frequency excisions shows varying grades of tissue destruction in these distant areas, and according to physical principles will demonstrate more pathologic insult than the tissue removed by the active electrode, for the simple reason that the current penetration in the underlying tissues is greater than that in the tissue removed. In the cautery removal the opposite is true.

Owing to the inherent quality of electric currents to produce heat in tissue, and due to the fact that these currents exert a deleterious effect upon the tissue well away from the site of burning, it is extremely essential that surgeons who are employing them should recognize their inherent dangers and exercise every precaution in modeling their technic. Bearing these points in mind it is absolutely necessary, in prostatic resection, to shift the scene of activity from one portion of the gland to another in order to de-

viate the paths of current, to avoid accumulative heating, and not to concentrate on any one segment except for a short period. It is hightly important that the minimum cutting current be applied for a minimum of time. If bleeding should occur it should be controlled wth coagulatng currents, whch are far less penetratng and damaging. Often the cystoscopist is misled in interpreting the coagulation picture as giving evidence of a severe reaction, when in reality the damage is much more superficial than the clean appearing surface resulting from the cutting current. If simple coagulation (not mass coagulation) is effected at one-third the current value employed for cutting, only one-ninth the heat will be produced. It is signally important to allow a proper cooling time between cutting strokes.

Since it is impossible to remove tissue, with any of these heating methods, particularly the high frequency, without leaving paths of necrosis in their wake, it becomes us to exercise care in the application of technic, and also to be equally judicious in the amount of tissue removed at any one sitting. The larger the field of operation, the greater the chance of complications and the burden of healing. The healing processes at the bladder neck under these conditions are somewhat hampered by bladder motion, which has a tendency, through its contractions, to disseminate infection and to unplug vessels. It seems evident that late secondary hemorrhages, a complication more commonly found following high frequency electric resections than with other methods, has its explanation in the discharge of the first two zones of necrosis, previously described, and the relief of tissue support from the underlying normal zone with the unplugging of healing vessels as the exudate passes away.

Another important feature to be remembered, in the conduct of high frequency operations, is the possible influence of penetrating heat upon the vessel sphincter. It seems highly possible that incontinence following these operations may be the result of devitalization of the sphincter through excessive heat. Urinary extravasation may result from the same process, provided the burning is carried too close to the surface of the gland.

On account of the tendency of the current to concentrate through exudative areas, or to follow electrolytic material which might be present in the rectal contents, it is necessary for the operator to

safeguard his patients by careful observation of these factors before operation.

Removal of prostatic obstruction by cautery or by methods which involve very mild coagulation followed by excision of tissue or by cold cutting procedures followed by coagulation seems unquestionably to possess less inherent dangers than methods which employ any type of high frequency cutting.

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NEPHRECTOMY FOR MALIGNANT DISEASE OF THE KIDNEY

SUPPRESSION OF URINE AND DEATH FOLLOWING MASSIVE DOSES OF X-RAY

FRANCIS R. HAGNER, M.D., and (by invitation) S. R. COLEMAN, M.D.

Washington, D. C.

The following case is presented to call attention to the possible deleterious effects of irradiation on the function and anatomic structure of the kidney.

The patient, a white man, forty-five years old, was admitted to Mt. Alto Hospital on May 24, 1932, suffering with left renal colic. The pain was quite severe in the left flank, but it did not seem to radiate to the groin or genitalia. One-half grain of morphine was given, which brought relief, and no further acute pain was experienced thereafter. The patient also complained at the time of admission, as well as later, of a moderate, steady pain in the upper back in the region of the scapulæ. His general health seemed to be good. He was well nourished and of fairly good color. His temperature was 100.5 degrees, his blood pressure 124/86, and the blood chemistry was 34.2 N.P.N. and 57 per cent P.S.P. in two hours. The differential test of phenol-sulphone-phthalein showed: Time of appearance from right kidney, three minutes; from the diseased kidney, three minutes. The total output was two-thirds from the right kidney and one-third from the affected kidney. Urinalyses showed heavy trace of albumin, a few red blood cells and a few hyaline casts. The result of the examination of the heart and lungs was negative.

Daily urinalyses were done and were, for the most part, negative, except that on occasions a slight trace of albumin was seen and an occasional hyaline cast. There was present in the urine from time to time, microscopic blood, but no gross blood was seen. A genito-urinary study revealed a mass present in the left flank, which was palpable and visible in the x-ray and was apparently attached to the lower pole of the kidney. Retrograde pyelogram outlined this mass more definitely, and the left pelvis was seen to be considerably distorted in the lower portion. Conclusions drawn were that the patient had a tumor involving the lower pole, probably nephroma.

After consultations with Dr. E. A. Merritt and Dr. H. H. Young, it was decided to give massive doses of x-ray over the left kidney with the view to lessening the danger of metastasis and in the hope of

reducing the size of the tumor preparatory to surgical removal. Accordingly, 300 milliampere minutes were given daily for four days beginning June 15, 600 milliampere minutes being given posteriorly and 600 anteriorly. The distance was 70 cm., screened with 0.5 mm. of copper and a 1 mm. aluminum filter. During the treatment the right kidney region was protected and was outside the x-ray field. The patient had the usual reaction to the x-ray therapy, namely, loss of appetite, weakness, loss of color, and a general bad feeling.

Twenty-four days after the last dose of x-ray was given, the kidney, with a large tumor of the lower pole, involving nearly the whole organ, was surgically removed under ethylene anesthesia (July 12). The kidney was adherent, and some hemorrhage occurred at the time of removal. Pathologic study of the specimen showed the growth to be a primary carcinoma, arising apparently from the tubular portion of the kidney. For ten days following the operation, the patient seemed to be making good progress, but on the tenth day he developed complete suppression of urine, although he had been given large amounts of fluid. The first twenty-four hours following the nephrectomy the recorded output of urine was 260 c.c., the second twenty-four hours, 570 c.c., and the successive daily output from then until the time of the patient's death was as follows: 1250 c.c., 520 c.c., 750 c.c., 780 c.c., 900 c.c., 450 c.c., 160 c.c., 0 c.c., 75 c.c., 145 c.c., 180 c.c., 516 c.c., 430 c.c., 404 c.c. Urinalyses done on July 28, 29, and August 1, showed from a trace to three-plus albumin, no blood, and from an occasional cast to a few granular ones. On July 28, N.P.N. was 230, and creatinin, 11.1. On July 29, the N.P.N. was 250, and on August 1, 291. The blood pressure was not high, being 148/70. The patient failed to respond to appropriate treatment and died a uremic death, August 2. Unfortunately, permission for an autopsy was not given; hence, there is no pathologic report on the remaining kidney.

A report of both experimental and clinical observations made in an article entitled "The Relative Sensitivity of the Kidney to Irradiation" appears in *Radiology* of February, 1927. The authors are H. P. Doub, A. Bolliger, and F. W. Hartman, of the Departments of Roentgenology and Pathology, Henry Ford Hospital, Detroit. They state that in a recent report of experimental work on dogs it was demonstrated that a fatal nephritis could be readily produced by application of hard x-rays through the body wall and that this result was accomplished both with single massive doses and with repeated small doses. They further state:

"Chronic diffuse nephritis of the combined interstitial and vascular type as produced by irradiation of the kidney through the abdominal wall has been uniformly obtained, often with relatively small single applications. This lesion is progressive in proportion to the initial damage, as demonstrated in functional and histologic studies. The progressive course is dependent upon the initial

destruction of the epithelium, absence of regeneration, prompt and extensive fibrous replacement and sclerosis of blood vessels and glomeruli. As a result of the lack of this repair process the kidney is perhaps more susceptible to complete anatomic and functional change than any other organ considered."

In connection with their experimental work, clinical observations were made on two cases. One was a white male, aged forty-five, with no other symptoms of nephritis than a trace of albumin in the urine and a phthalein output of 43 per cent at the beginning of treatment. After sixty hours of x-ray for lymphosarcoma the urine was of constantly low specific gravity and contained a moderate amount of albumin with numerous hyaline casts. The blood chemistry was high. Urea nitrogen rose from 12 to 30 mgs. per 100 c.c. of blood, and the blood pressure rose from 140/70 to 195/105.

The second case was one of a white female, aged sixty, who showed a trace of albumin in the urine, phthalein of 45 per cent in two hours, and a blood pressure of 120/80 at the time deep therapy was instituted following surgical removal of carcinoma of the pylorus. Ten months after the completion of the first course of deep therapy over the upper abdomen, the urine showed a moderate amount of albumin and many coarsely granular casts. Phthalein output was zero. Non-protein nitrogen was 150 mgs., urea nitrogen 74.2 mgs., and uric acid 7.15 mgs. The blood pressure rose as high as 230/140. The patient died in uremic coma.

In addition to the experimental and clinical observations, a statistical study was made by these gentlemen through correspondence with other roentgenologists and pathologists. Out of 208 replies received, sixteen were positive, that is, anatomic changes and impairment of function were produced by irradiation. In the conclusion of this article it is stated that the kidney is the most susceptible organ considered as far as anatomic changes and loss of function are concerned, that the direct irradiation of the kidney is shown to produce nephritis with hypertension in clinical cases as well as in the experimental animal, and that such direct irradiation should be avoided, especially in the young individual.

Though radiologists familiar with this particular case are divided on the question of the effect of irradiation on the function of the remaining kidney, the majority feel that it did have a deleterious effect. It seems to us that the delayed complete suppression of the urine, which did not occur until the tenth day after operation,

cannot be accounted for solely by the increased load thrown on the remaining kidney, as we well know that, following nephrectomy, the greatest call is made on the other kidney immediately following the operation.

As there is so little literature on this subject, it would be most interesting to observe the effect of irradiation on the function and anatomic structure of the kidneys in those patients treated for abdominal malignancy. In this connection, the thought occurs that the kidney function may be impaired in certain of these cases even though impairment is masked by the general condition of the patient.

We are unwilling to take our observations on this case as conclusive. We offer them as suggestions, in the hope of prompting further investigation on the subject of the sensitivity of the kidneys to irradiation.

DISCUSSION

DR. JOHN H. CUNNINGHAM (Boston, Mass.): I am interested in Dr. Young's paper as I have operated upon three patients with filariasis in this country, and have seen many patients with this disease in several of the West Indies Islands, Trinidad, and Colombia. Also, I have a further interest in this subject as the first year I was a member of this Society (1906), Dr. Robert Taylor read a paper on filariasis and I well remember my trepidation in discussing it.

I would like to take the liberty of touching upon some of the features that Dr. Young has not mentioned.

As you probably know, the disease is brought about in man by the sting of the mosquito—the mosquito being the intermediate host, and man the definite host. Female mosquitoes of the genus Culex (C. fatigans) and the Anopheles (A. niggorimus) draw the filarial embryos from the infected individual. The embryo undergoes a metamorphosis within the mosquito, which, when complete, takes a position in the proboscis, where it remains until the mosquito feeds upon some warm-blooded vertebrate, at which time the parasite enters the definite host. After entering the human body, the filaria finds its way into the lymphatic system, where it remains and develops into the matured parent worm.

In the majority of individuals afflicted, ill effects are produced by the obstruction of the lymphatics, and the greater proportion of such manifestations are associated with the generative and urinary systems; and, furthermore, the parent worm is most often here located. The parent worms produce obstruction directly or indirectly in the lymphatic circulation. While it is rare that the worms produce occlusion of a lymph channel, their presence results in secondary changes, thickening the lymphatic walls and narrowing their lumina. By thrombosing lymphatic channels there is a rise of lymph pressure in the occluded vessels, resulting in varicosities and lymphatic edema. The practical point in all surgery is that one must get the parent worm to overcome this lymph block; and all surgery is directed toward that end. In many

instances, it cannot be attained, the parent worm being located in the thoracic duct. When they are in the inguinal nodes, a great deal can be done by surgery.

My first patient, operated upon in 1904, was, like Dr. Young's patient, from Colombia. He presented himself with a lymph scrotum the size of a large coconut, with masses in both groins the size of the fist. Embryos were constantly present in the blood at night and disappeared during the day. We made an extensive block dissection of both groins and the spermatic cords. In fact, Professor Wolbach and others watching the operation believed that I had not left enough blood supply to nourish the testicles. A pathologic study of the tissue showed it to be composed mostly of tortuous dilated lymphatic vessels. The parent worms were not observed in twenty-eight blocks of tissue examined. However, they must have been removed as the patient has never had more embryos in many studies of the blood which were begun twelve days after operation and have been repeated occasionally during the past many years.

In spite of the small amount of blood supply left in his vas, he had four children after he returned to Colombia; by a second wife, two more, and when I last visited him three or four years ago in Cartagena, he had just had another baby by his third wife. Incidentally, he became President of Colombia, but not the father of his country.

The second case was also from Colombia. We did find the parent worm in this case. He was cured locally and the embryos disappeared from his blood.

The third case, which was much more advanced (and all my cases were more advanced than Dr. Young's illustrations portray), was very extensive. We did not find the parent worm and he did continue to have embryos in his blood.

A practical surgical point which gives the best indication regarding success or failure to produce a cure is determined at the time of division of the highest point of the varicosity. If the escaping fluid is serous, we are above the obstruction; if chylous, we are below it.

DR. WARD J. MACNEAL: I appreciate very much the privilege of appearing before this Society at this time. I shall confine my remarks to discussion of Dr. McCarthy's excellent paper.

I have a few lantern slides which serve to illustrate three features of bacteriophage; first, the original observations of Twort of the moth-eaten appearance on plate cultures. This is the original observation of bacteriophage action and the presence of this agent in the culture causes these so-called plaques or areas of absence of culture to appear after the culture is started.

(Slide) Here is a similar phenomenon illustrated in tube culture. These are tubes in which a wire wet with bacteriophage was drawn up through the center of the culture.

(Slide) We have next an illustration of its behavior in an experimental animal. This rabbit received an intravenous injection of a large dose of staphylococcus and a few hours afterwards a dose of bacteriophage was given intravenously and it was killed three hours after that. One observes the staphylococci are not dissolved in these circumstances, but are phagocyted by the cells in the liver.

(Slide) This is another animal, showing a precisely similar phenomenon. So I would contrast the behavior of the agent in the animal body with its behavior in the test tube or in the plate culture. They are not identical, and I think it has been a great misfortune that certain workers in this field have assumed that one could immediately transfer to the animal body the findings in the test tube, that identically the same thing would occur. That is untrue, I am sure.

(Slide) One cannot transfer immediately to the human body what happens in animals. This happens to be the clinical chart of a patient who had a stone removed from his ureter at that point, on May 29. This gentleman is a friend of many of the persons in this room. He had his drain removed. He did very well until he began to have some chills with a staircase temperature. He had a positive blood culture. So bacteriophage in the wound was started at this point. He seemed to do better right away.

Three years ago, at the time this patient was treated, bacteriophage was regarded as a very dangerous thing. We were so afraid to use it that we stopped almost immediately when he got better. He went along better for a time but later, he had another positive blood culture, so we started bacteriophage again. All together he had about a quart of this material poured into his surgical wound. He had some transfusions. He made a recovery, but subsequently had an osteomyelitis of one of the vertebral bodies that made him

remain bed-ridden eight or nine months. He is now back at work practicing surgery.

(Slide) This is the chart of another patient who had a chill, a transfusion, another chill and then several severe chills. At this time it was thought wise to apply bacteriophage therapy. It is not a urological case, but a case of pelvic thrombophlebitis following an abortion. After the administration of bacteriophage, the temperature went to 107 and then fell rapidly. Bacteriophage was given on three more days. The blood culture became negative. The patient, after a prolonged convalescence, left without any sign of disease whatever except the right leg was about one-half inch greater in circumference than the left as a result of the thrombophlebitis.

(Slide) Here are charts of three patients; first one was an old man who had a large amount of pathologic disturbances in his body, heart, and joints. Various other disturbances included a diseased prostate which was removed at this time. Following that he had positive blood culture, a succession of chills and another blood culture, with 100 colonies of coli per c.c. of blood. About that time it was thought wise to try bacteriophage therapy. We started with 0.5 c.c. intravenously and gradually increased it to 75.8 cubic centimeters injected in one day, and it was planned to continue through the night with 10 c.c. doses each hour. Two were given. The patient died the next day. Evidently we did not influence at all the course of the disease by bacteriophage therapy.

The next patient, a woman who had a positive blood culture outside the hospital, was sent in from the outside and was admitted after this blood culture had been found to be positive. She was comatose when admitted on July 28, and when she wasn't in coma, she was a raving maniac. Intravenous bacteriophage therapy was started. She received 0.6 c.c. the first day and later 0.5 c.c., all intravenous doses. Later she was given 1 c.c. Her temperature, in spite of this therapy, or perhaps along with it, came down to normal. Her mentality cleared up and she was up and around in a chair on the eighth of August and walking on the ninth. She walked out of the hospital on the eleventh.

The third patient, a nurse, had a severe pyelitis, but a negative blood culture. She was given intravenous bacteriophage and after the very first dose, she chilled for twenty-five minutes. The temperature went to 105½ and dropped immediately afterward. The

urine showed 26,000,000 bacteria per c.c. She received intravesical therapy and the colonies dropped down immediately. Since she left the hospital we have had two check-up urines—collected, I may say, without a catheter, in deference to Dr. McCarthy's remarks—which have shown no bacteria whatever. This method of collection is more acceptable to the patient.

I have attempted to show you hastily three things: The way in which this agent behaves (1) in the test tube, (2) in the animal, and (3) in the human body. Its efficacy in urology or any other special field of medicine remains to be decided by work of specialists in that particular field.

DR. J. DELLINGER BARNEY (Boston, Mass.): I think Dr. Caulk's contribution to our knowledge of diathermy and high frequency is very valuable. I would like to ask him to tell us as definitely as he can what he thinks of the comparative value of the tube machine as against the spark-gap machine.

DR. HUGH H. YOUNG: I should simply like to state that my cases were entirely different from Dr. Cunningham's. None of my cases had elephantiasis or lymph scrotum. None of them had micro-filaria in the blood. Cases due to the filaria sanguinis-hominis are usually characterized by very large scrotums. We therefore think our three cases were due to another filaria, the onchocerca-volvulus.

DR. JOHN R. CAULK (St. Louis, Mo.): May I have Mr. Harris answer Dr. Barney's question? I don't pose as being a physicist.

MR. WILBUR HARRIS (St. Louis, Mo.): Our experiments indicate that the same amount of current passing through the same sample of tissue produces equal temperature effects. However, cutting may be effected with the tube machine with less current than would be employed in the spark-gap machine. The current from the tube machine is controlled in a more positive way and does less damage to tissue for this reason, as well as for the more important reason of employing a lesser current value. The spark-gap machine delivers a cutting current which must be used at a higher value in amperes, which causes this type of cutting to be attended with less hemorrhage and deeper tissue damage.

In choosing his instrument the surgeon must decide which is more important, the hemostasis gained in using the spark-gap machine, or the additional tissue damage caused. This is evidently not a question for a physicist to decide.

DR. JOSEPH F. MCCARTHY (New York City): I had hoped to refrain from discussing prostates, but find it rather difficult. Dr. Caulk's findings are not in conformity with those of Corbus and Hennessey, of Memphis. They reported that the depth of penetration is 0.2 of a millimeter with the tube type machine as opposed to a considerably greater depth with the spark gap. I wonder if Mr. Harris has taken oscillographs of these currents?

MR. HARRIS: No, I have not.

DR. MCCARTHY: If you had, you would not describe the tube type machine as producing only an undamped current, because it has many damped characteristics. A study of these currents with the oscillograph will serve to clarify present misconceptions of their characteristics.

The position I have consistently maintained has been the advocacy of a superficiality of coagulation, with punctate sealing of the particular bleeding points. If one is excessively concerned about operative oozing, it may be well that he employ a spark-gap type of machine. But it seems to me that the purpose of the operation is largely defeated by the use of this type of current, because of its difficulty of control. The tube type of machine is rapidly superseding the spark gap, at least the present tendency of technicians and manufacturers seems to so indicate. Coagulation with the tube machine is much more superficial—the cutting is more cleanly done. Isolated bleeding points are sealed focally and not at the expense of the surrounding tissue, and urethral convalescence is much shortened thereby.

We will probably develop along the lines of superficial type of cutting supplemented with a compression bag at the time of operation, retaining it in position three or four minutes beyond the normal physiologic clotting time of the patient, the isolated active bleeders being focally sealed with the hammer-head coagulating electrode.

We haven't enough clinical background to warrant a definite stand on this technical departure, but we have been very much com-

forted by the results in a series of cases. In any event, it is our present position in this evolutionary procedure. To me, the use of the spark-gap current in so delicate and highly adsorbable a membrane as the deep urethra is comparable to watering a New York apartment house flower pot with a fire hose.

PRESIDENT FOWLER: Dr. Caulk, do you care to answer that?

DR. CAULK: I wish to say that Mr. Harris knows physics. His Ph.D. work concerns particularly oscillographs. He has developed an instrument of his own. Our work seems absolutely definite that heat is responsible for the damage and that it occurs with both types of machine.

SECOND DAY, MAY 9, 1933

BONE METASTASES FROM CARCINOMA OF THE URINARY BLADDER

ROGER C. GRAVES, M.D., and (by invitation) RAYMOND E. MILITZER, M.D.

From the Urological Clinics of the Pondville Hospital at Norfolk (Massachusetts Department of Public Health), and the Carney Hospital, Boston, Massachusetts

A review of the subject of bone metastases from carcinoma of the urinary bladder, as discussed in the textbooks and current literature, reveals that proved cases of this condition are extremely rare. Some authors describe the occurrence of such metastases but fail to present histologic proof of the direct association between the tumor in the bladder and the lesion in the bone. There is ample reason for this, in that the final proof in most instances can be obtained only by post-mortem examination. X-ray evidence alone is not sufficient. Moreover, it is true that even when autopsy permission has been granted, the bone specimen may not be taken from the exact area shown to be involved in the films. When the lesion is small, and where there is no gross tumor in the bone, it may easily be missed by the pathologist in his routine investigation. We would suggest that sometimes this difficulty might be obviated by an immediate x-ray photograph of the specimen before it is accepted as representative tissue.

It is the purpose of this paper to review the subject of secondary deposits in bone from bladder cancer, and to suggest that such deposits probably occur more often than is commonly supposed. A marked difference of opinion is expressed in the text-books. Young[10] states that "metastasis from bladder tumors is moderately late, as a rule. Metastasis apparently is usually by the blood stream, as noteworthy growths in the regional lymphatic nodes are seldom seen. These may be involved, however, late in the disease. There is no marked site of predilection for metastases from bladder neoplasms but any tissue of the body may be involved. Search for metastases must therefore be thorough."

Colston[2] writes that "dissemination by way of the blood stream

is said to occur more frequently than by the lymphatic channels, the liver and lungs being then the sites of predilection, although any tissue of the body may become involved. Metastasis to bones does undoubtedly occur, but in our experience it is rare, which is an important difference between bladder tumors and tumors of the prostate, as in the latter the bones of the pelvis and lower spine are often early extensively involved." Barringer,[1] on the other hand, states that "metastases to the bones are fairly common, and rare to the liver, lung, pleura, kidney, inguinal and axillary lymph nodes." Again, according to Geraghty,[4] "metastases to bones seem to be quite frequent in carcinoma of the bladder, being similar in this respect to carcinoma of the prostate. There seems to be a peculiar tendency of these malignant growths to set up secondary growths in the bones, and metastases to the vertebræ are not infrequent. The liver, lungs, and spleen are favorite sites for metastatic processes."

Kelley and Burnam[7] do not mention bone involvement from bladder cancer, but state that "carcinomata of the bladder often grow slowly and do not form metastases early. When metastases take place they are usually in the regional glands or in the lungs." Kaufman[6] emphasizes the necessity for complete x-ray study of the skeletal system when planning a radical operation for extirpation of carcinoma of the bladder. However, he then minimizes the importance of this statement by saying that "cancer of the bladder is limited practically throughout its course to the walls of the bladder and seldom, if ever, metastasizes, although the vast majority of cases present infiltration widely spreading and finally invading the perivesical and pelvic structures. Visceral and skeletal metastasis, which is so common in cancer of the prostate, is rare in cancer of the bladder." Ewing[3] states that "metastases are not common, but have been observed in liver, lung, pleura, kidney, and inguinal and axillary lymph nodes."

The clinical contributions to this discussion are limited. Kretschmer[8] in 1922 reported five cases of bladder tumors metastasizing to bones, and deserves credit for arousing interest in the subject. Three of the cases were studied at autopsy, and in none did he cite specific microscopic proof of the relationship between the bladder and bone lesions.

Wells[9] in the same year reviewed the literature, and added a case

of primary papillary carcinoma of the urinary bladder, with a secondary papillary carcinoma of the sternum. Microphotographs of the two lesions were presented. In addition, there were metastases to the left axillary lymph nodes, lung, right kidney and liver, and

TABLE I

Case No.		1	2	3	5	6	Total
Hospital No.		4968	1308	2796	4979	665282	—
Age		52	59	65	68	55	—
Sex	Male	Yes	Yes	Yes	—	Yes	4
	Female	—	—	—	Yes	—	1
Duration of symptoms to time of discovery of bone metastases		2 yrs.	3 mos.	10 mos.	6 mos.	5 yrs.	3 mos. to 5 yrs.
Type of tumor	Infiltrating	Yes	—	Yes	—	—	2
	Papillary	—	Yes	—	Yes	Yes	3
Microscopic diagnosis		*Epi. Ca.	*Epi. Ca.	*Epi. Ca.	†Tra. Ca.	—	—
Autopsy		Yes	Yes	—	Yes	—	3
Bones involved	Pelvis	—	Yes	Yes	Yes	—	3
	Vertebrae	—	Yes	Yes	—	—	2
	Ribs	Yes	Yes	—	—	—	2
	Femur	—	Yes	—	Yes	—	2
	Humerus	—	Yes	—	—	—	1
	Radius	—	—	—	—	Yes	1
	Scapula	—	Yes	Yes	—	—	2
Other metastases	Liver	Yes	No	—	No	—	1
	Lungs	Yes	No	—	Yes	—	2
	Lymph Nodes	Yes	No	—	No	—	1
	Local Extension	Yes	No	Yes	No	—	2
Type of metastases	Osteoclastic	Yes	Yes	Yes	Yes	Yes	5
	Osteoplastic	—	—	Yes	Yes	—	2

*Epidermoid Carcinoma. †Transitional Cell Carcinoma.

also in the right first and fourth, and left first and fifth ribs, and in the ilium.

We have reviewed forty-three consecutive cases of carcinoma of the bladder observed during the past five and one-half years at the Pondville Hospital. In four of these cases there was roentgenologic evidence of bone metastasis, and in one of them we were able to obtain histologic sections of the affected bone. There was a fifth patient with areas of bone destruction in the pelvis which we felt to be probably direct extension of growth rather than metastatic deposits. A sixth case with clinical and x-ray evidence of bone involvement from carcinoma of the bladder was observed at the Carney Hospital and is included in this report. In two other patients, changes were observed in the bones—in the skull and pelvis in one instance, and in the pelvis and lumbar spine in the other—which were thought to be due to osteitis deformans or Paget's disease, and not to malignant metastasis.

Table I serves as a summary of the important data of the five cases with definite evidence of osseous metastases. Four of the patients were males. The age of the group ranged from fifty-two to sixty-eight years. The duration of symptoms, to the time bone metastases were noted, varied from three months to five years. This variation should dispel the impression that metastasis occurs only in the late stages of the disease. The metastases were osteoclastic in every instance. In two of the cases there was also evidence of new bone formation. Kretschmer found evidence of new bone formation in one of five cases. Attention is called also to the fact that in the two complete autopsies of our group, malignant deposits in the lungs were found in both cases. This raises a question concerning the path of dissemination in bladder cancer. It is probably lymphatic in the greater number of cases but that metastases are blood borne in many instances is indicated by the not uncommon involvement of lung, liver and bone.

REPORT OF CASES

Case 1.—This patient, an English mason, fifty-two years old, was admitted August 6, 1932, complaining of pain in the back. The onset of illness was two years before, with hematuria. This recurred every few months for about one year. In February, 1932, a diagnosis of carcinoma of the bladder was made at another hospital. Radium was

implanted into the growth by suprapubic operation. Since then he had developed severe backaches, urinary frequency, and urgency.

Fig. 1. Roentgenogram of the pathologic specimen in Case 1, showing involvement of the rib and the soft tissue tumor.

Physical Examination.—The patient was thin and anemic. There was marked tenderness in both costovertebral angles. The left kidney was palpable and tender.

Cystoscopy.—This was attempted, but accurate inspection was not possible because of a spastic bladder filled with blood clots and necrotic material.

Roentgenograms.—Films of the pelvis and lumbar spine, on admission, were negative for metastases. On September 16, 1932, six weeks later, a film of the chest showed the presence of a destructive process in the right fourth rib.

Clinical Course.—Hematura continued in moderate amounts. An opening appeared in the suprapubic scar and urinary drainage was reëstablished through this sinus. The temperature was irregularly

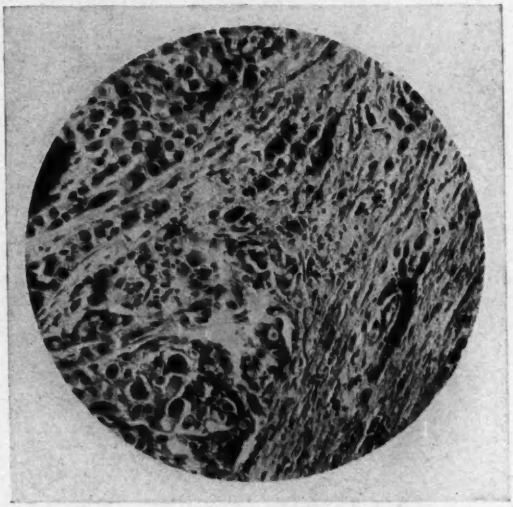
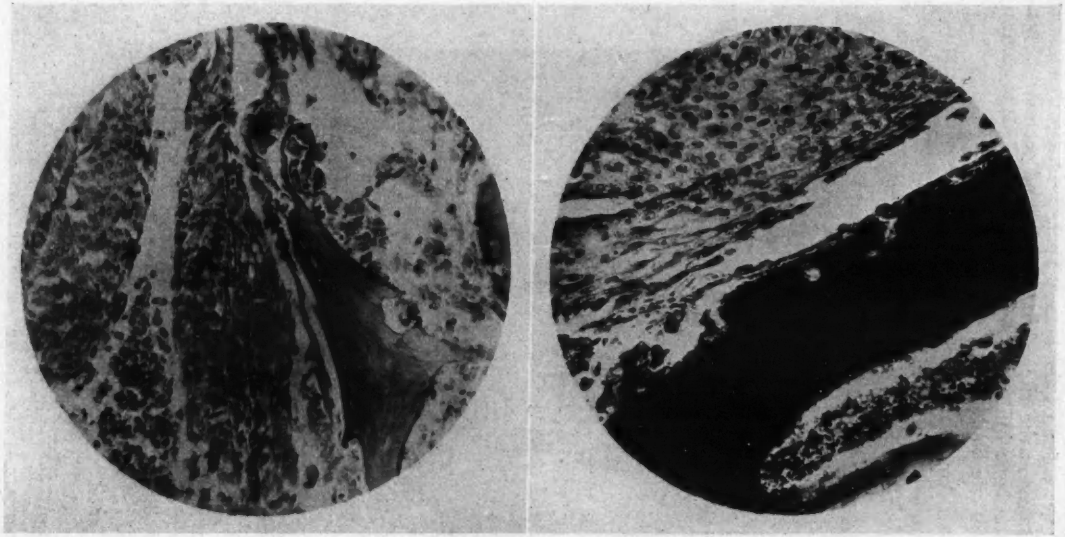


Fig. 2. Section of the bladder from Case 1. The wall of the bladder is extensively infiltrated with tumor cells of epithelial origin.

elevated; the fever was sometimes high. The patient had marked anorexia and began vomiting. A transfusion was given. Two weeks before death a fusiform swelling was noted involving the fourth rib in the right anterior axillary line. This rapidly increased in size until it was 6 cm. long and 5 cm. wide. The non-protein nitrogen rose from 31 mg. on admission to 90 mg. and the patient died September 26, 1932. Post-mortem films of the ribs verified the previous x-ray observations (Fig. 1).

Autopsy.—A necrotic neoplasm of the bladder was found, involving almost the entire mucosa. Histologically, this was an epidermoid carcinoma, grade III (Fig. 2). There were metastases to the liver, lungs, and right fourth rib. The tumor in the rib was a soft, greyish mass



Figs. 3 and 4. Sections of the tumor in the rib from Case 1. The bone is invaded by epithelial cells similar to those found in the bladder.

extending from the third rib above to the fifth rib below, and fully 6 cm. along the course of the bone. There was a pathologic fracture of the fourth rib at the site of the tumor, and sections (Figs. 3 and 4) showed the bone infiltrated with tumor cells of the same type as those found in the bladder.

Case 2.—An American wool-sorter, aged fifty-nine, admitted April 25, 1929, complaining of sharp pains in the right side of the abdomen and flank, of ten weeks' duration. Hematura was observed on one

Fig. 5. Case 2. Roentgenogram showing narrowing of the eleventh dorsal vertebra.

occasion, two weeks before entry. The daily urinary output had diminished to about 500 c.c. since that time.

Physical Examination.—A well developed and well nourished male. The liver edge was faintly felt. The right kidney was barely palpable and tender. The prostate, by rectal examination, revealed slight induration near the apex of the gland, and in the region of the right seminal vesicle, but there was nothing to warrant a diagnosis of carcinoma in these areas.

Cystoscopy.—There was a papillary tumor, its surface covered with many blood clots, just inside the sphincter on the right lateral wall of the bladder. The ureteral orifices were not obstructed. The prostatic outline was normal except for a slight median bar posteriorly.

Roentgenograms.—The entire skeleton was examined. The skull was negative except for some increase in the convolutional markings

suggestive of increased intracranial pressure. There were no visible metastases in the lung fields. The ribs were riddled with minute foci of diminished density, probably metastatic. The eleventh dorsal vertebra was definitely narrowed and wedge-shaped, with the preservation of the intervertebral spaces above and below (Fig. 5). The pelvis and both femora were studded with small, sharply defined, punched-out areas, characteristic of malignant metastases (Fig. 6).

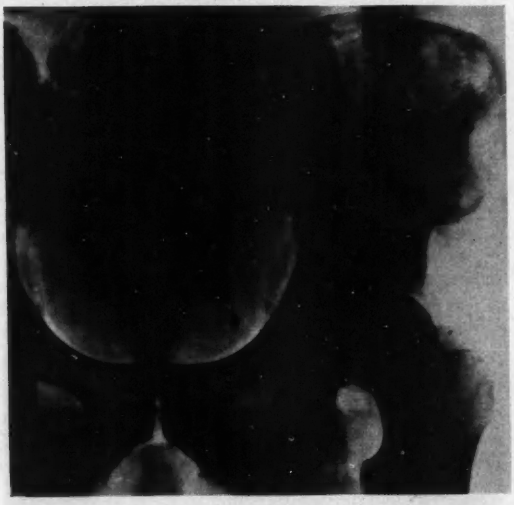


Fig. 6. Case 2. Roentgenogram showing numerous punched-out areas in the pelvis and upper end of the femur.

Post-mortem films of the upper extremities and shoulder girdles revealed similar areas of bone destruction in the scapulæ and upper ends of both humeri (Fig. 7).

Clinical Course.—On May 7, 1929, the patient suddenly developed a complete flaccid motor paralysis of both legs. The level of anesthesia was at the umbilicus. The non-protein nitrogen rose from 34 mg. on admission to 67 mg. one week before death. The patient became distended and incontinent, began vomiting, and died June 4, 1929.

Autopsy.—An abdominal incision only 6 inches long was permitted. There was a small localized abscess on the posterior surface of the bladder. A papillary growth, 2 centimeters in diameter, was found projecting into the cavity of the bladder from the right lateral wall. No local extension of the growth, or metastases to the lymph nodes or

liver could be found. The prostate was grossly negative.

Histologic examination of the tumor revealed a papillary carcinoma. Sections of the prostate showed hypertrophy of the glands and stroma, and chronic prostatitis. A specimen of bone, selected at random from one of the pubic rami, and without x-ray control, failed to show metastatic disease.

Case 3.—This patient, a white American male, aged sixty-five, was

Fig. 7. Case 2. Roentgenogram showing area of destruction in the left humerus.

admitted December 10, 1930, from another hospital, complaining of frequency of urination.

Past History.—Eight years ago he had an excision of a carcinoma of the lower lip, and an upper neck dissection. Six months later he was given deep x-ray therapy to each side of the neck. One year later the lip was treated with radium.

Present Illness.—Symptoms began ten months previous to admis-

sion, with hematuria, dysuria, and increasing urinary frequency. In May, 1930, at another hospital, an epidermoid carcinoma of the bladder was treated by suprapubic fulguration and the implantation of radium. There is no record of any x-ray examination before operation. The patient was admitted to Pondville Hospital because of persistent urinary symptoms.

Physical Examination.—An elderly, emaciated male. There was no sign of recurrence of carcinoma in the lower lip or neck. A tender

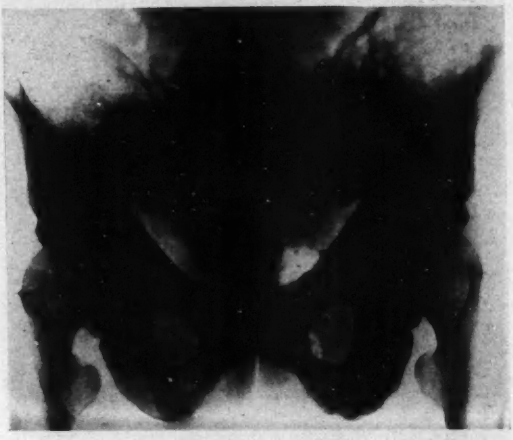


Fig. 8. Case 3. Roentgenogram showing extensive areas of bone destruction and hyperplasia particularly in the left innominate bone.

mass was palpable just above the symphysis pubis. By rectum, the prostate was normal in contour, smooth, and within its capsule.

Cystoscopy.—The bladder was very intolerant and vision was obscured by free bleeding. Heaped-up irregularity could be seen on the right lateral bladder wall suggesting recurrent growth of the infiltrating type.

Roentgenograms.—Films of the pelvis and lumbar spine on December 21, 1930, revealed "an extensive pathologic process involving the entire left innominate bone with similar but less extensive changes in the right ilium. The process is characterized by a pronounced over-production of bone, combined with some bone destruction (Fig. 8). The changes are consistent with a hyperplastic type of metastatic malignancy. The lumbar spine shows some increased density in the first

and third lumbar vertebræ (Fig. 9). The twelfth dorsal vertebra also appears dense." On January 8, 1931, films of the skull were negative. There was increased density of the eighth dorsal vertebra. The acromial process and lateral margin of the right scapula were very dense.

Clinical Course.—The patient failed gradually, became markedly emaciated, and died April 4, 1931. There was no autopsy.

Fig. 9. Case 3. Roentgenogram showing increased density in the first and third lumbar vertebræ.

Comment.—This is a case of multiple malignancy, one lesion being primary in the lower lip, and the other in the urinary bladder. The lesion in the lip represented a seven-year clinical cure. Since carcinomata of the lip almost never metastasize to bones, the bone lesions were believed to be metastases from the tumor of the bladder.

Case 4.—This patient, an American steam-fitter, aged fifty-nine

was admitted April 27, 1931, complaining of hematuria of one year's duration. Ten months before entry a suprapubic fulguration of a carcinoma of the bladder was done at another hospital. For six months he had had persistent pain in the right hip, radiating down the right leg.

Family History.—One brother and one sister died of cancer of the stomach.

Fig. 10. Case 4. Roentgenogram showing area of destruction in the right ilium along the pelvic brim.

Physical Examination.—A well developed but pale and emaciated white male. There was a healed suprapubic scar, and a hard mass 6 centimeters in diameter, deep in the pelvis on the right side. This could be felt rectally. The prostate was small and benign.

Cystoscopy.—There was extensive slough and free bleeding in the region of the trigone, especially on the right.

Roentgenograms.—Films of the lumbar spine were negative. On the right side of the pelvis adjoining the acetabulum, but not involving the hip joint, were irregular areas of decreased density (Fig. 10).

Clinical Course.—The patient failed steadily and died July 26, 1931, three months after admission. There was no autopsy.

Comment.—While this case has been included in the report because of the obvious bone involvement, it is agreed that the dis-

ease in the ilium in this instance was probably direct extension of growth, rather than metastasis.

Case 5.—This patient, an Irish woman, aged sixty-eight, was admitted August 9, 1932, complaining of hematuria of six months' duration. This was accompanied by urinary urgency, frequency, and dysuria.

Physical Examination.—A well nourished but very pale woman.

Fig. 11. Case 5. Roentgenogram showing hyperplastic type of metastases in the right ilium and left pubis and a destructive process in the right ischium.

The abdomen was normal, except that the right kidney was easily felt.

Cystoscopy.—The urine was very bloody and contained many clots. Prolonged irrigation made satisfactory inspection possible. A large papillary mass, covered with blood clots, was found on the right lateral bladder wall. The right ureteral orifice could not be seen.

Roentgenograms.—A film of the pelvis showed an irregular area of increased density in the right ilium, interpreted by the roentgenologist as an area of metastasis of the hyperplastic type (Fig. 11). A similar area was found in the left pubis adjacent to the symphysis.

There was a fairly large destructive process in the right ischium. A film of the chest was negative.

Clinical Course.—Treatment for the marked secondary anemia was instituted with some improvement. Anti-luetic therapy was administered because the Wassermann reaction was positive. Two weeks after admission, the patient complained of pain in the right knee. An

Fig. 12. Case 5. Roentgenogram of the right knee showing a destructive process in the lower end of the femur.

x-ray film of this region showed the presence of a destructive process in the lower end of the femur, together with some bone condensation (Fig. 12). She suddenly became comatose, and died October 23, 1932, ten weeks after admission.

Autopsy.—The bladder contained a tumor mass 4.5 centimeters in diameter, originating in the region of the trigone, involving the right ureteral orifice, and extending to the opening of the left ureter. Microscopically this was a transitional cell carcinoma. There was local extension of the tumor to the vagina and cervix uteri. Metastases were found in the regional lymph nodes and lungs. Obstruction of the ureters accounted for bilateral hydronephrosis and hydro-ureter.

Sections of the ilium were obtained, but failed to reveal any tumor. Where there is no gross swelling in the bone, the difficulty in obtaining a specimen exactly from the involved area can be understood. Permission to obtain a specimen of the lower end of the femur was not granted.

Case 6.—An American customs official, aged fifty-five years, was admitted to the hospital August 13, 1928, complaining of difficulty and pain in urinating. His illness began five years before with dysuria, relieved for a time by medication. During the past year he had noticed

Fig. 13. Case 6. Cystogram showing a large filling defect involving the left half of the bladder.

occasional hematuria, and more recently much free bleeding and many clots. He also complained of pain in the left forearm.

Physical Examination.—A moderately well nourished man of fifty-five, complaining of marked urinary distress. Multiple, non-tender superficial nodules could be felt under the skin of the forearms and thighs. The right kidney was low and palpable, but not enlarged or tender. The prostate was small and benign.

Cystoscopy.—The cystoscope was easily passed, but there was much free bleeding. In the left half of the bladder, blood clots and fringes of tumor tissue could be seen. There was no apparent prostatic obstruction.

Roentgenograms.—Cystograms revealed an extensive filling defect, consistent with malignant disease, involving most of the left half of the bladder (Fig. 13). Films of the left elbow showed complete destruction of the upper end of the radius (Fig. 14).

Clinical Course.—The patient was discharged home September 8, 1928, where he failed rapidly and died within a short time. His wife was insane, and permission for an autopsy could not be obtained.

In order to emphasize the fact that all bone lesions in patients with cancer are not necessarily metastatic, we include the reports of two additional cases in which the bone involvement was due probably to Paget's disease.

Case 7.—This patient, an American accountant, aged fifty-four, was admitted January 24, 1931, complaining of hematuria, dysuria, and loss of weight of one year's duration. Four months before admis-

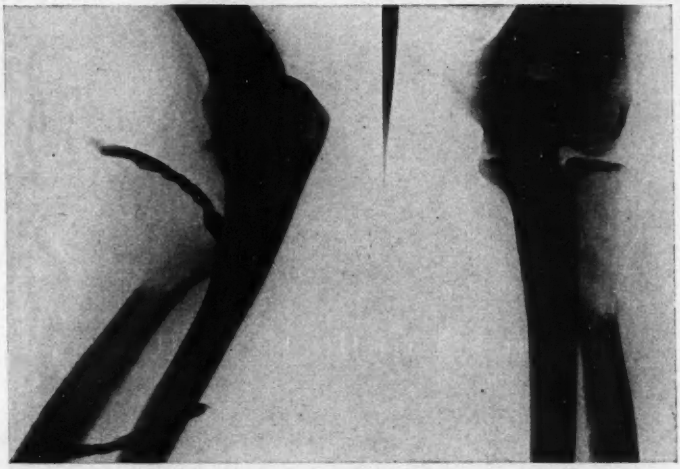


Fig. 14. Case 6. Roentgenogram of the left elbow showing complete destruction of the upper end of the radius.

sion, a suprapubic fulguration of an epithelioma of the bladder was done at another hospital. The growth at that time was said to be too advanced for resection. Postoperative x-ray treatments were given.

Physical Examination.—A tall, emaciated, white male. The right kidney was enlarged but not tender. Rectally there was a large, firm, uneven mass in the region of the bladder floor, and filling the right side of the pelvis.

Roentgenograms.—Examination of the pelvis showed considerable increase in density in the medial portion of the right innominate bone. Films of the chest, spine, and shoulder girdles were negative. The bones of the vault of the skull showed some mottled decreased density together with a number of areas of increased density (Fig. 15). Because of the appearance of the lesions, and the involvement of the

skull, a diagnosis of Paget's disease was made by the roengenologist. The patient died March 5, 1931.

Autopsy.—There was a large papillary tumor in the urinary bladder. Microscopically this was a transitional cell carcinoma of high-grade malignancy. There was thickening of the right innominate

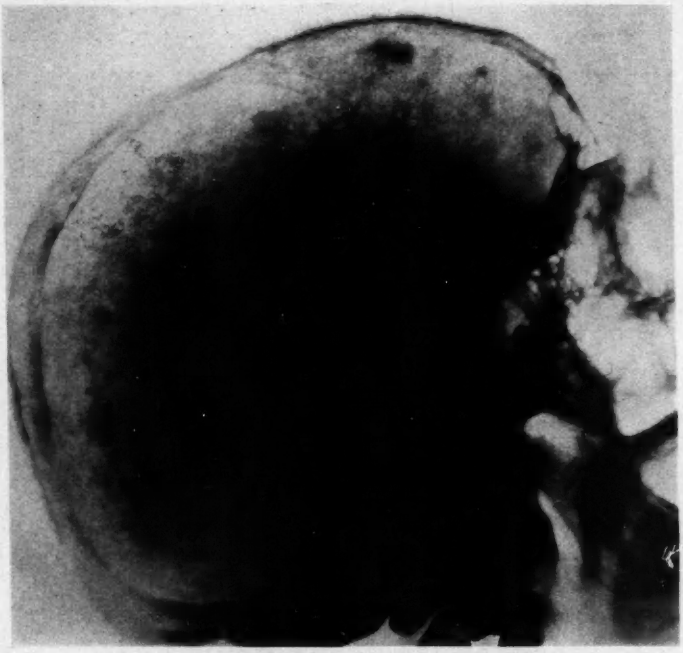


Fig. 15. Case 7. Roentgenogram showing mottled decreased and increased density in the vault of the skull.

bone just posterior to the anterior inferior iliac spine, but unfortunately, no specimens of bone were obtained.

Case 8.—An American carpenter, aged seventy-six years, was admitted February 14, 1931, with a history of increasing dysuria and hematuria of three and one-half years' duration. On October 20, 1927, at another hospital, a papillary carcinoma of the bladder had been excised through a suprapubic cystotomy. On January 13, 1931, at the same hospital, an emergency suprapubic cystotomy was done because of active hemorrhage. A large papillary tumor of the bladder was

found, and coagulated, but because of the bleeding it could not be removed entirely. The pathologic report at this time was squamous-cell carcinoma.

Physical Examination.—A well developed and well nourished elderly white male. There was a firmly healed suprapubic scar with a catheter emerging from a sinus near its mid-point.

Fig. 16. Case 8. Roentgenogram showing increase in density of the left innominate bone, probably Paget's disease. A roentgenogram taken two years later shows almost no change.

Cystoscopy.—A papillary new growth was seen arising from the left side of the trigone.

Roentgenograms.—Examination of the skull was negative. Films of the lumbar spine and pelvis showed pronounced increase in the density of the fifth lumbar vertebra, and also increased density of the left innominate bone (Fig. 16).

Clinical Course.—In spite of the x-ray evidence of probable metastatic bone involvement, on March 4, 1931, at Pondville Hospital, the bladder was re-opened. The tumor was electro-coagulated and radon seeds were inserted around the base of the growth. Biopsy confirmed the diagnosis of papillary squamous-cell carcinoma. The patient was discharged on April 22, 1931, after an uneventful convalescence.

He returned to the out-patient clinic for follow-up examination February 15, 1933, nearly two years after operation. His general condition was excellent and he had no complaints. On cystoscopy

there was a white scar, with some remaining slough at the original site of the tumor. There was no sign of recurrence. Films of the pelvis and lumbar spine showed changes identical with those originally described. Since there was practically no advance in the extent of these bone lesions in a period of two years, we believe that they are due, probably, to Paget's disease rather than to metastases from the bladder.

Comment.—The last case is particularly instructive. Clinically it represents an apparent two-year cure of carcinoma of the bladder. If the patient had been classified as inoperable two years ago because of the x-ray evidence of bone disease, he would undoubtedly long since have died of his cancer.

CONCLUSIONS

1. Metastases from carcinoma of the bladder to bones are more common than generally supposed.

2. Metastases may be few or widespread. Aside from the pelvis there seems to be no particular predilection for any bones. Search for metastases must therefore be thorough.

3. One case of carcinoma of the bladder with metastases to the lungs, liver, and right fourth rib, histologically proved is presented. In addition, four cases of carcinoma of the bladder with x-ray evidence of bone metastases are reported.

4. Osseous metastases from carcinoma of the bladder are usually of the osteoclastic type, but some cases also show osteoplastic changes.

5. Two cases of carcinoma of the bladder showing bone changes suggestive of Paget's disease are reported. Great caution must be observed in condemning a case as inoperable because of associated bone lesions.

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FIVE-YEAR RESULTS OF SUPRAPUBIC RADIUM IMPLANTATION INTO BLADDER TUMORS

EDWARD L. KEYES, M.D., F.A.C.S.

New York City

The case histories that form the basis of this paper constitute a continuation of the histories of thirty-one patients with bladder tumor treated by suprapubic implantation of metal capsules (which are referred to in the text as radons†) containing radium emanation. These thirty-one cases have been previously reported and the method of operation described.* They are the first thirty-one cases operated upon by me by this method. The operations were performed between December, 1925, and March, 1928. The five-year results of these operations are quite gratifying in spite of the fact that four cases have been included (4, 15, 16, and 17) whose initial treatments were made by resection (4) or by radium implantation through less satisfactory methods, two with glass seeds, two with steel needles containing radium element. These four patients have died of carcinoma.

Moreover, many of these patients received a lower dosage of radium than would be employed today. We now use 2 millicurie radons‡ in place of the 1 millicurie or 1.5 millicurie radons that we employed on so many of these patients. One case (Case 13) definitely had insufficient radiation. The tumor was controlled for two years. Quite possibly had a larger number of radons been implanted the ultimate result might have been better.

For these reasons and because of what seem more promising results obtained on patients who have been operated upon since this series, we feel that the results here presented are minimal.

In the previous report two deaths from operation are recorded: one, three days after suprapubic implantation of radium; the other a death due to ileus following resection of the bladder for persis-

†Journal A. M. A., 1933, 50:1765.

*Transactions of the American Association of Genito-urinary Surgeons, 1928, 21:137; Journal of Urology, 1927, 17:205; Arch. Franco-Belges de Chir., August, 1928.

‡Screen of 3 mm. gold.

tent tumor of the vault after repeated radium implantation had failed.

This is the only resection performed in the series and so excellent have been the results of radium implantation that in the intervening years but two cases have been resected and one submitted to total cystectomy. All other operable cases have been treated by radon implantation if too extensive or too malignant for fulguration.

RESULTS

In the previous report results were tabulated after dividing the cases into four groups: papilloma—and—Grade I, Grade II, Grade III, and Grade IV. The typing was done by a combination of clinical and pathologic observations somewhat similar to that employed by Dr. Barringer in 1928. In most instances, slides of the tumors were preserved and have been subsequently graded by the American Urological Association Carcinoma Registry. The results are instructive. Three cases (Cases 1, 2 and 3) that had been previously graded I, were placed by the Registry as a papilloma, a Grade II and a Grade III. The two cases (4 and 5) graded II were placed as Grades I and I-plus. The eleven cases graded III (6 to 17) were again graded III with four exceptions which were graded II. The fourteen cases graded IV (18 to 31) which grossly and palpably infiltrated the bladder wall with hard masses of tumor were regraded, as III and IV with one exception, graded as II and of interest as the only survivor in this group. A brief history of this patient seems worth repeating.

Case 29.—Male, sixty-seven years of age, intermittent hematuria two years. Bimanual examination revealed a vague resistance and thickening in the bladder region. Cystogram showed the bladder pushed to the left. Cystoscopy was interfered with by bleeding. There seemed to be an infiltrate all across the base of the bladder.

In March, 1927, under spinal anesthesia, the bladder was opened and "an infiltrating tumor was found which, when first seen, appeared as a papillary growth surrounding the urethra and growing chiefly from the right side of the trigone and adjacent bladder wall. Its base extended about 3x3 cm. to the right of and below the urethral orifice and all the way around in front of the urethra and about 2 cm. up the right side of the bladder along the line of the ureter. Thirty radons of 1 mc. each were implanted in the growth with counter pressure by finger in rectum to identify the depth of the growth, which in only one place seemed to need one radon deeper than another." The bladder, sutured

without drainage, broke open on the sixth day, and healed on the twenty-sixth.

In February, 1928, a recurrence occurred of a most malignant looking type on the opposite side of the bladder. The mucosa was lifted up and the tumor seemed to break through it. Into this, four radons, each containing 2.5 mc., were implanted through the cystoscope. Specimen was reported Grade II.

Repeated negative cystoscopies have been performed since that time, the last in September, 1932, five and one-half years after operation and four and one-half years since the operative cystoscopy. The patient reported himself well, by letter, in May, 1933.

It is interesting to compare the prognostic accuracy of the older methods of more or less combined clinical and pathological malignancy with the modern grading. According to the older classification there were eight tumors in Grades I and II. Of these patients only one died (12.5 per cent). There were eleven Grade III tumors; two patients died of operation and three of carcinoma, making an almost 50 per cent mortality. One of these patients lived three and one-half years, another three years from the original treatment. Thirteen of the fourteen clinically Grade IV patients died of carcinoma; one died after twenty-seven months, and one by suicide because of blindness due to wood alcohol. In the second patient (Case 30) the fistula was still open and very likely the tumor was still in him three and one-half years after operation. One remained well and working six years and then died of carcinoma, while the patient in Case 29, cited above, is the only survivor.

In contrast to these, the American Urological Association pathologic grading omits one of the cases as a papilloma (surviving) and seven as ungraded (five patients died of carcinoma, Case 22 in three months, Case 24 in four months, Case 27 in eleven months, Case 4 in two years, Case 30, suicide at three and one-half years, fistula still open and carcinoma probably present, while two survived and are well over six years) and classes the others as follows:

Two Grade I: One patient well after three and one-half years (cystoscopy) and then lost sight of; one patient well, five and one-half years.

Six Grade II: One patient upon cystoscopy was found free from tumor five months after operation and was then lost sight of; three others were well at the end of four, five and one-half, and six and one-half years; two died (Cases 15 and 16), each of whom

had the original treatment by radium element and not by radons.

Twelve Grade III: Three survivors, two operative deaths, seven cancer deaths (at intervals of five, seven, eight, thirteen, eighteen and twenty-seven months and three and one-half years), survivors well and free from cancer at five and one-half, five and one-half, and six years (the six-year survivor was graded III-plus).

Three Grade IV: All died of carcinoma, one at seven months, one at thirteen months, and one at six and one-half years (Case 31). This man had remained at work and supposed himself well for six years after the radium implantation.

There have been no deaths by intercurrent disease.

The mortality for the whole series (by operation, two; by carcinoma, 17) was 61 per cent, the five-year cures 29 per cent. Excluding the seven ungraded cases and Cases 15, 16 and 17, the treatment of which was begun by earlier methods, and the papilloma (Case 3, well six years), the graded cases are classified as follows:

Grades I and II: Six cases, no deaths. One cure verified five months, the others three, four, five (twice), and six years.

Grade III: Eleven cases, one operative death, seven carcinoma deaths, three cures followed over five years (mortality 73 per cent; five-year cures 27 per cent).

Grade IV: Three casses, all dead within six years.

The discrepancy between the results of the clinico-pathologic grading of 1928 and the American Urological Association grading, here reported, is not great in sum, but is important in detail. To this day I cannot clinically distinguish papilloma from Grade I, II or III carcinoma, nor, in the clinically infiltrating group, Grade II from III or IV. Case 29, cited above, seemed to me as malignant a case as I had ever seen. Grading and survival proved me wrong. Subsequent experience confirms the impression that tumors microscopically grouped under Grades I or II are almost as curable by radium as papilloma and should scarcely fall within the popular conception of cancer. Metastasis occurs so late that almost the most neglected cases should be curable by cystectomy.

Unfortunately, the majority of bladder tumors that have seemed to me malignant enough or extensive enough to merit open operation are of Grades III or IV (60 per cent of this series), and when these have become so extensive as to merit cystectomy, metastasis

may almost be assumed to be present, reducing even cystectomy to the rank of a palliative operation.

COMMENT

1. The American Urological Association Registry amply justifies its existence. It gives a sound basis for comparison between case reports and a sound measure of progress in our therapy.

2. All epithelial tumors of the bladder graded as I or II should be attacked as curable by fulguration, radon implantation or cystectomy unless moribund or inoperable for other reasons.

3. Grade III has a bad prognosis. We can report but 23 per cent five-year control. Most of the cancer deaths occur in the first two years.

4. The prognosis of Grade IV is even worse. Yet one patient has remained at work and apparently well for six years—and then died of cancer.

5. No attempt has been made to compare cystoscopic fulguration or radon implantation with suprapubic radon implantation. During the period within which these thirty-one patients were operated upon, six patients were seen who were deemed too far gone for operation, radons were implanted through the cystoscope into seven others, and cystoscopic fulguration was sufficient to cure "about a dozen" others (for these I have no exact figures). Thus, during this period more than half my bladder tumor patients submitted to suprapubic implantation of radons. Thanks to the practice of suturing the bladder without drainage, the postoperative mortality and discomfort are slight. Thirty-seven radon implantations are here reported with but one postoperative death. (The second postoperative death followed resection of the bladder.) The atrocious postoperative spasms that follow the implantation of glass seeds do not occur unless more than twenty radons are implanted. Twenty-seven of the operations were followed by no more discomfort than is to be expected after any cystotomy. The six patients who required more than one operation submitted to the second operation without comment.

6. Comparison between resection of the bladder and radon implantation for the treatment of the more malignant tumors cannot be attempted on the basis of the cases reported here. Cure of a localized tumor is possible by either method. Resection is not

applicable to tumors about the trigone or bladder neck, though these present no peculiar difficulties to radon implantation. Ureteral re-implantation does not have to be considered. The operative mortality is much lower, the stay in hospital so much shorter as to pay for the radium. In this series eleven were drained, and and of the twenty-six sutured without drainage, eleven broke open. For the fifteen who did not leak, the average postoperative stay in hospital was fifteen days, for the others the postoperative fistula stayed open, on the average, twenty-three days. It is to be hoped that the durability of radium cure is no longer questioned. I have reported two patients relieved for more than ten years.*

7. At the other limit of malignancy, in the treatment of tumors of Grades I or II, the high frequency current competes with radium for use by suprapubic section just as it does for cystoscopic use. Indeed, the current offers the most convenient method of removing the growth preliminary to implantation. For the treatment of minor degrees of malignancy the choice is, perhaps, of no great importance. But whether applied through the cystoscope or through the suprapubic wound, radium destroys malignant tumors that fulguration does not control.

CASE HISTORIES

Case 1.—Grade II. Ch., male, seventy-two years old, with symptoms two years, was operated upon in February, 1926. Five radons of 2 mc. each were implanted. There were no postoperative treatments. The last cystoscopy was done September, 1927. The patient was last heard from in September, 1932, well, six and one-half years after operation.

Case 2.—Grade III. Me., male, seventy-four years old, with symptoms six weeks, multiple tumors, was operated upon in April, 1927. Twenty radons of 1.5 mc. each were implanted. There was no postoperative cystoscopy or treatment. The patient was well in September, 1932, five and one-half years after operation.

Case 3.—Papilloma. Schr., male, sixty-four years old, with multiple tumors, was operated upon in December, 1926. Twenty 1 mc. radons were implanted. The last cystoscopy was done in February, 1933. The patient remains well six years after operation.

Case 4.—(Not graded.) Cr., female, eighty-two years old, had her bladder resected for tumor in 1918. In 1922, and the following years, fulguration and cystoscopic radium implantation were used. The pa-

*Surg., Gynec. and Obstet. (February), 1933, 56:462-463.

tient came to me in 1926 with a small, soft papillary tumor about the right ureteral orifice. After several months of vain cystoscopic efforts, in August, 1926, the bladder was opened and five radons containing 1.5 mc. each were implanted. She was a difficult patient. The tumor reappeared in October, 1927. In spite of cystoscopic treatments they spread over the bladder and in January, 1930, she died of carcinoma, almost three and one-half years after the operation.

Case 5.—Grade I. Mo., male, thirty-nine years old, with symptoms one year, had an extensive growth in the bladder and posterior urethra. Operation was performed in December, 1926. Eleven 1 mc. radons were implanted. Small recurrence was fulgurated three and one-half years after operation. Six months later there was evidence of active pulmonary tuberculosis; the patient had lost 10 pounds. The last cystoscopy was done in May, 1933. There was no tumor. The patient is well with tuberculosis controlled.

Case 6.—Grade I. Ro., male, fifty-five years old, with symptoms one year, had extensive multiple tumor. Operation was performed in October, 1926. Eleven radons of 1.5 mc. each were implanted. Numerous postoperative fulgurations of five distinct recurring tumors were given, one of them within the urethra. The recurring bladder tumors were cleared up by November, 1929, but the urethral tumor persisted. Four hundred millicurie hours of radium emanation, in a catheter tied in the urethra (125 mc.) in August, 1929, partially controlled this and a month later it was destroyed by fulguration. November, 1929, a recurrent bladder tumor was burned off, and in April, 1930, bladder and urethral tumors were again burned. In October, 1931, one-stage suprapubic prostatectomy was done; fistula closed in fourteen days. Incontinence of a few drops of urine followed operation and persisted. In December, 1932, cardiac decompensation prohibited the patient's getting about. Last cystoscopy was done in November, 1932; no tumor. The patient, last seen May 1, 1933, is completely inactive because of his heart, but empties bladder, holds urine two to four hours, no symptoms of tumor five and one-half years after operation and three years after the last cystoscopic treatment.

Case 7.—Grade III. On., female, seventy-six years old, died operative death.

Case 8.—(Not graded.) Gr., female, sixty-seven years old, had a tumor of the lower end of the ureter and bladder following nephrectomy for papillary carcinoma of kidney pelvis. Cystoscopic treatment failed. Operation was performed in July, 1926. Twelve 2.5 mc. radons were implanted. No postoperative treatments were given. Cystoscopy showed negative results seventeen months after operation. The patient was last seen well, six and one-half years after operation.

Case 9.—Grade III. Schw., male, fifty-five years old with symptoms

seven months, was operated on in May, 1927. Fifteen 1.5 mc. radons were implanted. No postoperative treatments were given. Cystoscopy was negative and the patient was well in November, 1932, five and one-half years after operation.

Case 10.—(Not graded.) Bul., male, 60 years old, with symptoms six months, was operated on in November, 1926. Fourteen 1.5 mc. radons were implanted. No postoperative treatment was given. Last cystoscopy was done four years after operation. The patient was well six years after operation, November, 1932.

Case 11.—Grade II. Ca., male, forty-eight years old, had tumor of the bladder and urethra. Symptoms were of seven months' duration. Cystoscopic treatment irritated the bladder. Operation was performed in November, 1926. Fourteen 1.5 mc. radons were implanted. Urethral tumors were fulgurated in May, 1927. Arteriosclerotic bladder ulcer was found (post-radium) in March, 1928, but no tumor. The patient was well in December, 1930, four years after operation.

Case 12.—Grade II. Hi., male, forty years old, with symptoms twenty years, had tumors of the bladder and urethra. He was operated upon in March, 1928. Twelve 1.5 mc. radons were implanted. The patient was lost sight of after a negative cystoscopy in August, 1928.

Case 13.—Grade III. Por., female, fifty years old, with symptoms one year, was operated upon in January, 1926. The tumor was excised with cautery and three platinum radons of 3 mc. each placed in base at least 3 cm. apart. This was one of the first patients operated upon. It was recognized that the amount of radium was inadequate but no more was at hand. Six weeks later cystoscopy was negative, but in May a recurrence was seen and in June, three radons of 1.5 mc. each were implanted. Thereafter, cystoscope showed no tumor in September, 1926, and September, 1927. But in August, 1928, a carcinomatous lymph node appeared above the left clavicle, and cystoscopy showed a deep carcinomatous ulceration to the right of the fundus. No treatment was given. The patient died in June, 1929, three and one-half years after operation.

Case 14.—Grade III. Ba., male, fifty-four years old, with symptoms six months, after cystoscopic treatment failed, was operated upon in December, 1926, when 20 gold radons, 1 mc. each, were implanted. Three months later cystoscopy showed tumor, and thirteen radons of 1.5 mc. each were implanted (operation) into the same growth. Cystoscopy was negative in 1930. The patient was last heard from alive and well in January, 1933, six years after operation.

Case 15.—Grade II. Pa., male, fifty-four years old, with symptoms

two months, was treated first in September, 1925, by suprapubic section and implantation of six steel tubes each containing 3 mc. of radium element. A recurrence at the same spot was controlled by implantation through the cystoscope in December, 1925, of three platinum radons containing 3 mc. each followed by five fulgurations in the next three months.

The bladder growth thereafter remained healed, but in Octobr, 1926, a urethral neoplasm appeared and this, in spite of many fulgurations and the urethroscopic implantation of one 1.5 mc. radon in February, 1927 and three 1.5 mc. radons in September of the same year, continued to grow and extended to the prostate. The patient died in September, 1930, of secondary carcinoma of the prostate, five years after his operation.

Case 16.—Grade II. Fra., male, forty-four years old, with symptoms fifteen months, was first treated in November, 1925, by the implantation of ten tubes each containing 2.5 mc. of radium element. Tumor was uncontrolled. In October, 1926, fifteen radons of 1.5 mc. each were implanted; in January, 1927, five more by cystoscope, and in February, 1927, the bladder was re-opened and twenty-five 1 mc. radons implanted. This resulted in severe radium burn and caused a vesico-rectal fistula, but did not control the carcinoma of which the patient died in June, 1929, three and one-half years after the first operation.

Case 17.—Grade III. Po., male, forty-seven years old, with symptoms eighteen months, died in spite of much fulguration, three suprapubic implantations of radium (the first with glass seeds) and a resection of the bladder vault. Death was due to ileus after resection of the bladder, but carcinoma of the bladder was found in the specimen, and at post-mortem examination no metastasis was found. Treatment was begun in February, 1924. The patient died in May, 1927.

Clinically Infiltrating Tumors

Case 18.—Grade III. Buc., male, fifty-four years old, had carcinoma of the larynx two years previously, and eighteen months before operation hematuria and diagnosis of carcinomatous ulcer. He refused operation until February, 1926, when six platinum radons, containing 2.5 mc. each, were implanted in an extensive tumor covering the trigone and left bladder wall, its base about 6 x 8 cm. in diameter. This implantation was obviously inadequate. The patient died of carcinoma nine months later.

Case 19.—Grade III. Bir., male, forty-four years old, with symptoms four months, was operated on in February, 1928. Operation revealed a carcinomatous ulcer of the base of the bladder 6 x 3 cm. Thirty gold 1 mc. radons were implanted in two layers. The patient died of carcinoma in five months.

Case 20.—Grade III. St. Jo., male, fifty-six years old, with symptoms four years, was operated on in September, 1926. Operation disclosed an infiltrating papillary growth, its base 3 cm. in diameter, extending from above the urethra to the vertex. The infiltration was at least 1 cm. thick, the projecting tumor of considerable size. Fifteen 1.5 mc. gold radons were implanted. This was inadequate. The patient considered himself well until March, 1927, when his symptoms recurred. I refused to re-operate upon him. He was re-operated on elsewhere and more radium implanted. He died in June, 1927, nine months after the first operation.

Case 21.—Grade IV. Scha., male, fifty-nine years old, with symptoms seven months, was operated on in September, 1927. Five gold 1.5 mc. radons were implanted into the indurated base of a small papillary tumor situated near the right ureteral orifice. The bladder lesion was controlled, but the tumor extended into the pelvis and in April, 1928, seven months after operation, the patient died of carcinoma.

Case 22.—(Not graded.) Te., male, sixty-six years old, with symptoms four years, had bladder tumors which had been fulgurated. In October, 1926, operation revealed an infiltrating tumor surrounding the bladder neck and occupying the trigone. Twenty gold 1.5 mc. radons were implanted. In January, 1927, three months after operation, the patient died of carcinoma.

Case 23.—Grade III. Bier., female, fifty years old, had diabetes, with symptoms of bladder tumor six months. In September, 1926, operation revealed hard infiltration extending from vertex down the right side to the base. Perivesical fat was sclerotic. Lesions were 2 cm. wide and about 5 cm long. There were several secondary tumors. Fifteen gold 1.5 mc. radons were implanted with no benefit. In April, 1927, seven months after operation, the patient died of carcinoma.

Case 24.—(Not graded.) Da., male, seventy-two years old, with symptoms five months, was operated on in November, 1927. Operation revealed a tumor of the left side of the base of the bladder, its base 3 x 3 cm. in diameter. Twenty gold 1.5 mc., radons were implanted. Bladder symptoms were controlled but pains developed three months later in the left side of the pelvis, and in March, 1929, sixteen months after operation, the patient died of carcinoma.

Case 25.—Grade IV. De., female, seventy years old with symptoms one year, was operated on in February, 1928. Operation revealed an ulcerating infiltrating papillary tumor of the vault covering the major part of the right wall of the bladder. Thirty 1.5 mc. radons were implanted but were evidently inadequate. In May, 1928, four 2.5 mc.

radons were implanted by cystoscope, and in March, 1929, thirteen months after operation, the patient died of carcinoma.

Case 26.—Grade III. Fa., male, sixty-seven years old, with symptoms three or four years, was operated on in January, 1927. Operation first opened the peritoneum and revealed that the whole subperitoneal portion of the bladder was infiltrated with carcinoma, the tumor having originally doubtless been in the vault. Twenty gold 1 mc. radons were implanted into the bladder from its peritoneal surface without opening the viscus. A month later radiogram showed only 3 radons. The other had doubtless been pushed through the bladder wall and been lost. Accordingly the bladder was opened and 30 gold 1 mc. radons were implanted. These were evidently inadequate but the immediate result was surprisingly good. Before the second operation the patient had lost 31 pounds. He regained 21 pounds, and in November, 1927, cystoscope showed a much inflamed contracted bladder with an ulcer in the fundus but no definite tumor. He died of carcinoma without recurrence of his grave bladder symptoms in July, 1928, eighteen months after operation.

Case 27.—(Not graded.) Fl., male, sixty-four years old, with symptoms three months, was operated on in February, 1927. Operation revealed extensive infiltrating carcinoma of the left side of the bladder extending from the trigone half way to the apex. Seventeen gold 1 mc. radons were implanted. The operation gave no relief whatever. In January, 1928, eleven months after operation, the patient died of carcinoma.

Case 28.—Grade III. Ga., male, sixty-three years old, had symptoms of about one month's duration. In February, 1926, a tumor about 4 x 4 cm. in diameter at its infiltrated base was implanted with three platinum 2.5 mc. radons. Radiation was inadequate. Symptoms were relieved for a year. In May, 1928, twenty-seven months after operation, the patient died of carcinoma.

Case 29.—Grade II. (See text.)

Case 30.—(Not graded.) Bo., male, forty-three years old, alcoholic, syphilitic, had symptoms of bladder tumor of six months' duration. He arrived at the hospital in retention due to clots. In March, 1927, operation revealed ulcerating tumor of the right side of the bladder neck and edge of trigone, its base infiltrated and 3 x 4 cm. in diameter. Thirty-two platinum 1 mc. radons were implanted partly in two layers. Ischio-rectal abscess resulted and never healed. In August, 1927, cystoscope showed a granulating area in the region of the right ureter from which a specimen was reported carcinoma. Accordingly in October, 1927, operation was performed and nine gold 1.5 mc. radons were implanted. In March, 1928, suprapubic extravasation of

urine opened. In May, 1928, urination was painless; the patient had gained 10 pounds. He was urinating once at night and every three to four hours by day; still drinking heavily. In June, 1930, the local condition remained about the same. The patient was developing an alcoholic blindness and was overwhelmed with debt. He committed suicide.

Case 31.—Grade IV. Sm., male, fifty-two years old, had a perineal prostatectomy one year before for relief of hematuria, which was successful. Cystoscope showed a tumor to the right side of the bladder neck. In June, 1926, six gold 2 mc. radons were implanted into an infiltration 5 x 3 cm. on the upper quadrant of the right side of the bladder neck. In September, 1926, cystoscope showed several masses of tumor in this same region. The bladder was again opened and seven gold 1.5 mc. radons were implanted. In October, 1926, cystoscope showed one lesion persisting and through the cystoscope four gold 1 mc. radons were implanted. Thereafter the patient remained well and free from symptoms and was at work until the spring of 1932, when his bladder symptoms recurred, and his pelvis was found full of carcinoma. He died in August, 1932, of carcinoma, six years after his operation.

DISCUSSION

DR. HUGH H. YOUNG (Baltimore, Md.): As one has to limit himself, I will simply talk about Dr. Keyes' paper, which I think is one of very great interest. He and his co-worker, Dr. Barringer, have certainly done a great piece of work in showing the value of radium, implanted either suprapubically or through a cystoscope. They have been leaders in this field, and I think Dr. Keyes' paper today proves conclusively the very great value of radium when properly applied.

I have also used suprapubic implantation of radium for a number of years, and we have some extraordinary cases where infiltrating tumor in the region of the ureter and sometimes involving the edge of the prostate has been completely destroyed apparently and the patients are entirely well after a number of years (three to ten).

I do not, however, use a suprapubic incision for the application of radium as often as he does. I feel certain that many of these patients can be treated by intravesical application of radium with the cystoscope.

I would like to cite some twenty cases of malignant disease of the bladder that we have treated by the application of radium by means of various cystoscopic applicators which I have devised.

I would like to put into the record a series of twenty cases that have been followed from three to ten years. Many of these patients seemed to be perfectly inoperable and incurable by any means at the time they were treated. They were treated by the application of radium with these instruments and fulguration.

Case 1.—S. R., male, aged forty-nine, had hematuria three years before, and was fulgurated six times elsewhere. Cystoscopy revealed a tumor near the right ureter 1 cm. covered with slough. Treatment consisted of fulguration and radium and the tumor disappeared in six months. The patient's condition was followed five years, and cystoscopy showed him to be entirely well at the end of that time. Microscopic examination revealed infiltrating carcinoma.

Case 2.—Mrs. T. H. R., aged fifty-two years, came for treatment May 19, 1927. She had a history of hematuria for six months. Large

tumor, 8 x 9 cm., was found with extensive carcinoma invading the bladder. Treatment consisted of radium and fulguration. Five years later she was entirely well.

Case 3.—W. H. W., aged fifty-nine years, was admitted June 5, 1916, with hematuria of one month's duration. A large necrotic tumor right side of base was treated with radium intravesically and fulguration; 2,405 mgh. by bladder, 809 mgh. per rectum. The tumor completely disappeared in one year. Six years later the patient was entirely well.

Case 4.—Mrs. J. M., female, aged fifty-six years, was admitted July 30, 1924, with hematuria of six months' duration. Tumor 1.5 cm. in diameter was found near the left ureter. Microscopic examination revealed carcinoma. The tumor was destroyed, recurred, and was again destroyed by radium and fulguration. It recurred again, four times, and was destroyed by radium and fulguration. Specimen removed by cystoscopic rongeur after two and one-half years still showed carcinoma. Continued treatment, radium and fulguration, caused complete cure. There was no recurrence within a period of three years.

Case 5.—J. K., aged fifty, was admitted January 7, 1928, with hematuria of one year's duration. Malignant papilloma 3 cm. in diameter was treated with radium and fulguration. There were small recurrences for two years, and radium and fulguration were applied. The case was followed two years with no recurrence.

Case 6.—H. F., male, aged forty-eight years, was admitted November 6, 1919, with hematuria of four months' duration. Pedunculated tumor 1.5 cm. in diameter, near left ureter, was destroyed by fulguration and radium. There were several recurrences. The same treatment was followed with no recurrences after fifteen months. Eight years later the patient was well.

Case 7.—F. V., male, aged seventy-seven years, was admitted February 9, 1928, with hematuria of one month's duration. Five small pedunculated tumors, microscopically appeared as papillary carcinoma. Treatment by fulguration and radium was used, with complete disappearance, and later recurrence elsewhere for two years. The case was followed one year without recurrence.

Case 8.—D. M., male, aged sixty-four years, was admitted May 14, 1929, with hematuria of one month's duration. Sessile tumor, 2.5 cm. was found behind trigone, with infiltrating papillary carcinoma. Treatment consisting of radium and fulguration destroyed the tumor in four months. The case was followed four and one-half years with no recurrence.

Case 9.—T., male, aged forty-nine years, was admitted June 26,

1922, with hematuria of two and one-half years' duration. A very large tumor, covering the right side of the trigone and lateral wall was diagnosed papillary carcinoma. Treatment was by radium 1,000 mgh. and fulguration. There was a small recurrence, treated by radium, 400 mgh. There was no recurrence and seven years later the patient was reported well.

Case 10.—F. M., male, aged sixty years, was admitted January 24, 1924, with hematuria of three years' duration. Dr. Kretschmer found a tumor the size of an egg, which was fulgurated. A recurrent small tumor was also fulgurated. Later recurrences were treated by radium and fulguration. The case was followed one year, and after the last treatment there was no recurrence.

Case 11.—H. M. K., male, aged forty-two years, was admitted May 2, 1928, with hematuria of two years' duration. A large malignant papilloma, 5 cm. in diameter, was found, springing from the trigone. Treatment consisted of radium 1,200 mgh. and fulguration. There was no tumor after three months. The case was followed for four years with no recurrence.

Case 12.—A. T. T., male, aged sixty-seven years, was admitted March 2, 1928, with hematuria of two months' duration. A large sessile papilloma was adjudged nonmalignant, and suitable for fulguration and radium. Recurrence was seen after eight months. Radium and fulguration were used followed by complete cure. The patient was well three years after beginning treatment. Comment: This case shows the value of radium in addition to fulguration in cases of large benign growths.

Case 12.—J. K. T., male, aged sixty-five years, was admitted June 19, 1924, with hematuria of eight months' duration. Papillary carcinoma of the bladder, 4 x 2 cm. in size, was treated with radium and fulguration. There was no recurrence within six years.

The following patient, who was not treated by radium, but fulguration and then suprapubic resection and ligation of the ureter in another clinic, came to us four years later with recurrence. Papillary carcinoma was treated by intravesical radium, 400 mgh., and fulguration. Cystoscopy three months later showed the patient to be well. Three years later cystoscopy again, well.

Case 13.—A. H. S., male, aged thirty-six years, was admitted March 16, 1929, with hematuria of over a year's duration. Large papillary carcinoma was found surrounding the prostatic orifice, and sloughing. Treatment consisting of radium and fulguration was used, with complete destruction of the tumor in seven months. Cystoscopy two years later revealed no recurrence.

Case 14.—G. R. R., male, aged sixty-five years, was admitted June 17, 1924, with hematuria of fifteen months' duration. A large malignant papilloma of the right trigone was treated with radium 800 mgh. and fulguration. There was a quick disappearance of the growth. One year afterwards there was no recurrence.

Case 15.—F. M., male, aged fifty-five years, was admitted August 23, 1922, with hematuria of three months' duration. A large, rough, sloughing tumor of right lateral wall and trigone was diagnosed carcinoma with suggestion that it should be resected if radium failed. Radium 1,200 mgh. was applied and in two months most of the tumor had disappeared. Then fulgurations followed. Cystoscopy six months later revealed no tumor, but the prostate was indurated. Twenty deep x-ray treatments were then given. On September 5, 1924, cystoscopy and rectal examinations were made and the patient was pronounced well. One year later he was still well. This case has now been followed three years.

Case 16.—J. P. McC., male, aged fifty-five years, was admitted September 24, 1926, with hematuria of five months' duration. Large infiltrating carcinoma of the right lateral and posterior wall was treated with radium 1,000 mgh. and fulgurations. In four months all evidence of the tumor was gone. Specimen removed with rongeur was negative. Four subsequent cystoscopies showed no recurrence. The case was followed for two years.

We have elsewhere referred to the fact that after suprapubic excision apparently benign papillomata are apt to recur.

Case 17.—W. B. C., male, was admitted September 14, 1918, with hematuria of six years' duration. Cystoscopy showed a small papillary tumor excised elsewhere, with recurrence of hematuria in two years. Recurrences were seen with the cystoscope (two) on the trigone. Fulguration was done with subsequent recurrences followed by fulguration. There were no recurrences after one year. The case has been followed eight years and the patient is reported well. One cystoscopy.

The following case is one in which we used our second parallelogram and third rotating radium applicators. Each contained 200 mgh.

Case 18.—T. C., male, aged seventy years, was admitted March 1, 1915, with hematuria of one year's duration. Two papillary tumors 1.5 cm. in diameter, on the trigone, microscopically were pronounced malignant papilloma. Treatment consisting of radium 350 mgh. and fulguration resulted in complete disappearance in six months. After two years, cystoscopy revealed no recurrence and the patient was pronounced well.

Case 19.—J. H. J., aged sixty years, was admitted September 7, 1927, with hematuria of one month's duration. Malignant papillomata covering area 6 x 7 cm. in size was treated with radium 1,200 mgh. and fulgurations. There was considerable trouble with slough, but the condition was healed and cured after two years. After a follow-up of four years the patient was pronounced well.

Case 20.—K. R. F., male, aged fifty years, was admitted February 15, 1917, with hematuria of two years' duration. Two strawberry-like tumors 1 cm. in diameter at the vesical orifice and corner of the trigone were diagnosed, by Geraghty, as malignant. Treatment consisted of fulguration and later radium. Cystoscopy, eight months later, showed no tumor. Bladder was normal. Cystoscopy, four years later, showed no recurrence. The case was followed ten years by cystoscopy. No recurrence.

Case 21.—Mrs. S. M. R., aged fifty-eight years, was admitted October 30, 1917, with a history of vesical irritability and frequency of five years' duration, and recently hematuria. Two months ago a tumor discovered cystoscopically was removed, and found to be malignant. Cystoscopy revealed that just external to the right ureteral orifice there was an area 5 x 7 mm. in size which was occupied by minute papillomata, which Geraghty thought were benign, and could easily be removed by fulguration. The tumors continued to recur, and were treated intermittently by fulguration for three years, and then by cystoscopic applications of radium. The tumors continued to recur, and on January 22, 1923, five and one-half years after admission, cystoscopy showed a small papilloma projecting out of the right ureteral orifice. The tumor moved back and forth with respiration. To destroy this tumor the bipolar current was used and one electrode introduced into the ureteral orifice. Small papillomata near the bladder wall and vesical orifice also were destroyed. On October 5, 1926, eighteen months after the last visit, cystoscope showed a large tumor, which obscured the right ureter. It was treated by fulguration and applications of radium. On October 15, 1927, vaginal examination revealed a hard mass about the size of a golf ball in the region of the right ureter. The right kidney was enlarged. Cystoscopy showed a large necrotic area in the right corner of the trigone, and two small tumors adjacent. Impression: carcinomatous infiltration of ureter and bladder. Nearly two years later cystoscope showed large white slough but no active tumor in the bladder. The patient has not been followed since.

The particular point of interest in this case is that microscopic study of the tumors removed showed a benign papilloma, which finally invaded the ureteral orifice, and traveled up the ureter and ultimately became malignant.

I apologize for reciting this long list of cases, but as there is little positive evidence by case reports of definite cures in malignant diseases of the bladder, I was anxious to put these on record. I wanted also to back up Dr. Keyes' contention that radium is of great value in the treatment of malignant tumors of the bladder; in fact, I think it has enabled urologists to obtain finer results in the great battle against cancer than any other department of medicine.

DR. F. R. HAGNER (Washington, D. C.): There are two points that I wish to make: (1) It has been our experience that in malignant disease of the bladder, if the bony structure is studied, you will find metastases in bladder tumors of the bony structure almost as frequently as in carcinoma of the prostate. I suppose all of you have had the same experience. (2) We have had remarkable results in relieving pain in the bone metastasis from massive doses of x-ray. I can hardly recall a patient whom Dr. Merritt has treated who has not been relieved by massive doses of x-ray.

It has been our experience that where tumors are located on the anterior wall of the bladder at the edge of the prostate, and we have used radon seeds, the patients have tenesmus. We have for some years been using radium packs in these cases. We use 100 milligrams of radium filtered with 2 millimeters of platinum, cover it with gauze, put a string through it like a Hagner bag arrangement, and then cover that with a finger-stall, and this is pulled down against the prostatic orifice. Of course, it is applicable only where it comes in contact with the growth. The string is threaded through the urethra and a small rubber band is attached to a Buck's extension on the leg, which holds the pack in proper position. At the other end a string comes out through the suprapubic wound to facilitate its removal. In this way the pack will come in contact with the growth. The patient is given from 3,600 to 4,800 milligram hours of radium in this way. By this method we do not have the tenesmus that seems to occur when radon seeds are used. We have had some remarkable results from this type of treatment.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): I was glad to hear that Dr. Keyes' experience corroborates that of our own, namely, that gradation of the degree of malignancy in the tumor tissue is of vital importance in regard to prognosis. Not alone is it of value with prognosis, but it is also of help in the type of treat-

ment indicated. In other words, we would not think of fulgurating a Grade II or IV tumor, but we probably would do so with a Grade I or II. Likewise, radium would be employed in part or entirely with Grades III and IV.

As far as the relative merits of radium and other methods are concerned, our experience has not been as great with radium used alone as it might be. Occasionally, the results with radium were brilliant, but they were not uniformly good. More recently we have been using a combination of surgical diathermy with radium, which seems to me a much more thorough method than either, singly.

In a recent report of our experience in the treatment of several hundred bladder tumors, made by Drs. Counseller and Walters, the results emphasize the value of tissue gradation and surgical diathermy either with or without radium.

It also shows that another very important factor must be considered, and that is the follow-up treatment. In other words, it is essential that the patient be carefully watched after operation and urged to come back for re-examination at three-month intervals. In this way we get the recurrences very early, and the prognosis is greatly improved.

DR. H. L. KRETSCHMER (Chicago, Ill.): I would like to discuss Dr. Graves' paper for a moment. The subject has interested me for a long time because the general opinion seems to be that metastases to the bones in carcinoma of the prostate are common, whereas metastases to the bones from carcinoma of the bladder are uncommon. As a matter of fact, the late Dr. Geraghty made the statement that bone metastases never occur in bladder carcinoma. Before the American Urological Association some years ago, I reported three cases of metastases to the bone in three cases of carcinoma of the bladder, and called attention, at that time, to the fact that in these cases the tumors were very small, papillary, and had it not been for the fact that routine x-ray studies were made, the carcinoma metastases would have been overlooked.

Since then I have seen three cases of bone metastases, and I would like to mention them. They were all, as in the other cases, papillary carcinomas. One occurred in a man fifty-nine years of age who had had a suprapubic cystostomy and surgical diathermy for a large papillary carcinoma. He had received many fulgura-

tions before the operation and subsequently for the treatment of recurrence. He suddenly developed severe pain in the hip, and a swelling occurred in that region which increased very rapidly. X-ray studies showed large metastatic carcinoma involving the great trochanter and the femur.

After the onset of these metastases, the pain became excruciating, and, as the metastases increased very rapidly, death ensued in a few months.

The second patient was a young man of forty-seven who had been treated elsewhere by means of fulguration repeatedly without avail. He had had intravesical application of radium and deep x-ray, but the results were *nil*. He suddenly developed severe pain and swelling in the region of his pubes, and x-ray studies showed an absence of the descending ramus of the pubes, and the ascending ramus of his ischium and pubes rapidly melted away. Before he died, about half of his pubes was gone, but apparently it made no difference in his gait.

The third patient was a man of fifty-seven who had a malignant papillary tumor. The surgeon who saw him had planned to do a resection of the tumor. The tumor bled profusely. A routine x-ray showed the presence of a very large metastatic involvement of the ilium. This precluded an operation.

It stands to reason that if we would study these cases more carefully, roentgenologically, than we have in the past, we would undoubtedly find a larger number, thus proving that metastases to the bones in bladder carcinoma is not so rare an occurrence as is thought today.

Our cases as a rule have been of the destructive type, that is, osteoclastic. What is important to remember is that on account of the metastases to the bones in carcinoma of the bladder as well as bone sclerosis in carcinoma of the prostate, a vital point of differentiation from Paget's disease arises. We have not had that problem in our metastatic bladder carcinomas.

Dr. J. Bentley Squier (New York City): I would like to endorse what Dr. Kretschmer has said. At present I have a gentleman in the hospital who, a year ago, had his bladder opened for a papillary carcinoma of the bladder which had been thoroughly fulgurated by another surgeon, and following the fulguration he had a number of treatments of deep x-ray therapy. He came under my

observation about three weeks ago with a recurrence of this papillary tumor. Recurrence had been there for some time probably. He had already manifestations of bony changes in the pelvic girdle. The tumor, according to the pathologic diagnosis of the first surgeon, was a papillary carcinoma, and at present the pelvic girdle is very thoroughly shot with evidence of bone involvement. I am quite sure that there is not a possibility of doubt as to whether this bony involvement is Paget's disease or not, because it has been very thoroughly studied by a number of x-ray experts.

DR. KRETSCHMER: I forgot to answer Dr. Young's question. The last time I saw the patient, he was free of tumor, and this was several years ago.

PRESIDENT FOWLER: Dr. Russell Ferguson, who is associated with Dr. Barringer at the Memorial Hospital, is present, and I am sure the Association would like to hear from him with comments on Dr. Keyes' paper.

DR. RUSSELL FERGUSON (New York City): It has been my privilege to study the content of the bladder tumor registry annually and report the contents of it to the American Urological Association. Last year—I have not yet completed this year's study—there were 600 cases in the registry of which 154 had been treated more than five years previously. The figures on the five-year survivals for each grade at that time corresponded very closely to those reported in Dr. Keyes' series.

Grade I was 72 per cent five-year survivals; Grade II, 43 per cent; Grade III, 24 per cent; and Grade IV, 4 per cent. This year there are over 600 tumors in the registry, and the comment is interesting that the rate of growth of the bladder tumor registry up to date has exceeded the rate of growth of any other registry of national scope.

I think that the content of the registry is much more important from the standpoint of studying the natural course of events in various types of tumors than it is from the standpoint of grading or the choice of treatment. There is some very interesting material in the registry with regard to the course of events in multiple tumors of the bladder.

DR. ROGER C. GRAVES (Boston, Mass.): There is no confusion,

of course, with reference to Paget's disease in the bone deposits from carcinoma of the bladder when those deposits run true to the average form and produce areas of destruction in the bone. The confusion arises only when there is a hyperplastic type of bone lesion, such as is more common in the case of prostatic malignancy. That, of course, does not happen often in bladder cancer, and I mentioned it in my paper merely to present those cases in contrast and to call attention to the error that one might make in condemning a patient as inoperable because of an osteoplastic type of bone change.

PHYSIOLOGIC FACTORS GOVERNING TESTICULAR FUNCTION

WILLIAM E. LOWER, M.D., and (by invitation) D. ROY McCULLAGH, Ph.D., EUGENE L. WALSH, M.D.,* and W. KENNETH CUYLER, M.S.

From the Cleveland Clinic, Cleveland, Ohio

The literature on endocrinology is becoming so voluminous that it is practically impossible for any one person to keep pace with developments. Some of the new facts are of great significance, and when the whole maze of hormonal relationships is finally untangled, we shall find probably that clinical practices in various fields will have to be altered.

Today I shall confine my remarks to some things we have learned in our laboratories about the function of the testes. Everyone knows, of course, that the testes have both an exocrine and an endocrine function. The external secretion is dependent in some way on the internal secretion, but the converse is not true. This is demonstrated clinically in patients with undescended testicles. In ectopic testicles, spermatogenesis is impaired, according to Moore, because of the change in temperature. This, however, does not interfere with the endocrine function of the testes. Neither function of the testicles is present in the absence of pituitary function, for the testes, prostate and seminal vesicles all atrophy in hypophysectomized animals, as has been shown by various workers. It has also been shown that pituitary extirpation causes atrophy of the thyroid and of the adrenal glands.

Dr. Walsh, working in our laboratory, has performed some very interesting experiments on the effect of the testicular hormone, prepared from urine, on the male sex organs of hypophysectomized animals. After ablation of the pituitary gland, there was considerable diminution in the weight of the testes, epididymis, prostate and seminal vesicles. But when these animals received injections of the male sex hormone from the urine for about twenty days following hypophysectomy, the normal weights of all of these organs

*George W. Belcher fellow.

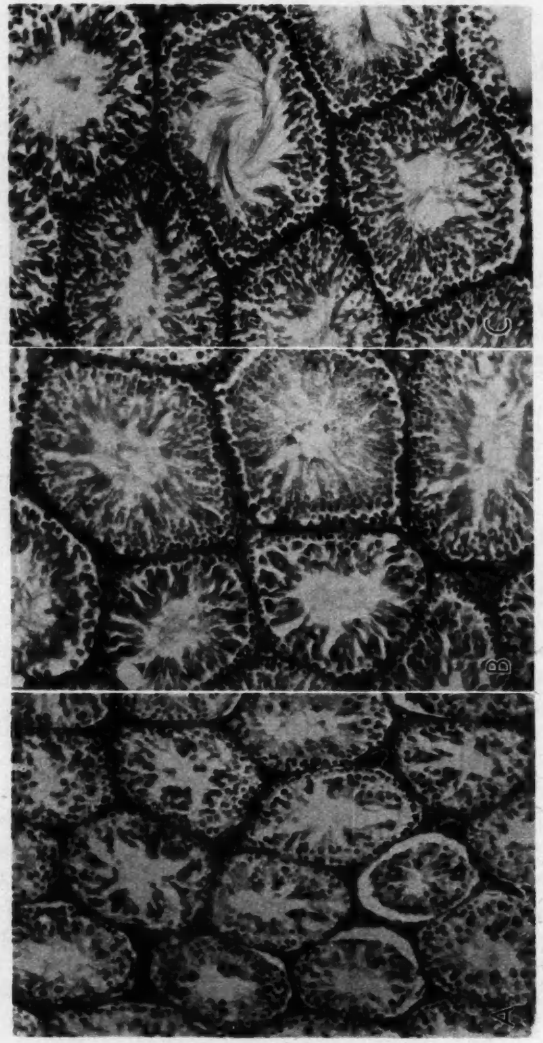

Fig. 1. Histologic sections of rat testes: *A*, Hypophysectomized, untreated; *B*, Normal control; *C*, Hypophysectomized and treated with male sex hormone.

were maintained as compared with normal rats used as controls. However, the thyroid and suprarenal glands remained atrophied. The complete absence of the pituitary gland in the animals operated on was verified by serial histologic sections at necropsy. Histologic sections of a testicle from a hypophysectomized rat and from a hypophysectomized animal to which injections of the hormone were administered are shown in Figure 1.

We had expected that injections of the male sex hormone would maintain the size and function of the secondary sex organs, as had previously been demonstrated in castrated animals, but an unexpected finding in these experiments was that the weight of the testes was maintained and that their spermatogenic function also was conserved, according to histologic examination. This finding contradicts the hypothesis of most workers in endocrinology that a secretion from a given organ does not influence the functional activity of that gland. The normal maintenance of the testicles in these experiments naturally raises the question as to whether or not the urinary extracts used may contain some pituitary substance in addition to the testicular hormone, but the physical, chemical and physiologic properties of the extract indicate that this is not the case.

Since these experiments were performed in our laboratory, our attention has been called to some work done by Freud last year in Amsterdam. He used male and female immature rats, which were both hypophysectomized and castrated, and showed that ovarian follicular extract and testicular extract stimulated and maintained the secondary sex characteristics respectively in these animals. From this, he concluded that the hypophysis is unnecessary in the maintenance by the sexual hormone of the secondary sex characteristics. Although our experiments were performed on mature, uncastrated animals, we reach the same conclusion, namely, that the pituitary is not essential for the maintenance of the secondary sexual functions, and in addition we have discovered that the testes can be maintained normally in the absence of the hypophysis.

THE OCCURRENCE OF METASTATIC MALIGNANT DISEASE OF THE KIDNEY

J. DELLINGER BARNEY, M.D., and (by invitation) E. ROSS MINTZ, M.D.
Boston, Massachusetts

Having been impressed not only by their own failure to find a case of metastatic malignant disease of the kidney either clinically or at autopsy, but also by the scanty reference in the literature to the question to be discussed, the authors decided to make as thorough an investigation of it as possible. The work was undertaken with minds open and entirely devoid of knowledge of the subject. The results of this study, while interesting, have so far failed to show any results that will be of material help to the clinician.

First of all it is important to consider briefly the known facts as well as some of the theories in regard to the mechanism of metastatic growth. For much of this information we are indebted to Ewing.

The appearance of metastases "may represent one of several events." Generally speaking, cancer spreads not only by way of the blood stream, but also by way of the lymphatics, in the case of rapidly growing tumors by the formation of lymphatic emboli; sarcoma less often spreads in this manner, but more commonly through the blood vessels. As Ewing says, "the abundance of thin-walled blood vessels, the presence of naked sinuses, and the tendency toward necrosis and hemorrhage rather than fibrosis may largely explain the predominance of blood vessel invasion by sarcoma as compared with carcinoma." Some tumors have a peculiar affinity for transportation through the venous system, either as emboli or by direct extension. Uterine chorioma is to be considered in this class.

That "retrograde transport" may occur not only in the venous but in the lymphatic system was recognized first by von Recklinghausen. Apparently conditions which disturb the weak forward venous flow in certain organs, of which the kidney is one, may transform the forward into a backward flow. The same conditions

may produce a similar disturbance in the lymphatics, although here it is apparently more essential that the main channel shall be occluded. Certain authors have described cases of metastases taking place through a patent foramen ovale, the so-called "paradoxic embolism" whereby large emboli can reach the aorta directly without going through the filter of the lungs.

In addition to the obvious channels for the transportation of tumor cells Böger has recently advanced the theory that in the kidney metastases may occur by way of the urinary stream in the ureter, the primary growth being in the case described situated in the rectum. That this may occur is not impossible, but Böger offers no proof beyond the fact that he was unable to explain the findings in his case in any other way.

We wish next to review briefly the anatomic factors by which renal metastases can take place. The vascular circulation of the kidney, both venous and arterial, is too well known to be dwelt upon. Suffice it to say that it is extraordinarily rich and complex. Not only that, but it is in closer touch, if we may use the expression, than is that of almost any other organ with the two great vessels of the body, aorta and vena cava. Because of this fact one might expect that metastatic malignancy of the kidney would be more frequent than the facts show it to be. While the vascular circulation of the kidney has been the subject of much study and is now well understood, the intricacies of the lymphatic system are not so well known. Cunningham's textbook of anatomy makes no mention whatever of the renal lymphatics (perhaps because of a typographical error). Gray's "Anatomy" describes three divisions of the lymphatics of the kidney, one within the renal substance, another situated beneath the fibrous capsule, and a third lying within the fat capsule. These three divisions, united more or less with one another, empty into the lymph nodes lying on either side of the aorta. The description in Morris' "Human Anatomy" agrees in the main with that given by Gray, but also states that the lymphatics of the suprarenals and of the upper portion of the ureters drain into those of the kidney. Here again one finds apparently two more possibilities for renal metastases, namely from tumors of the suprarenals and of the bladder.

In going over the literature we find surprisingly few references to the subject of metastatic malignancy in the kidney. Ewing has

called attention to the fact that uterine chorioma may produce retrograde renal metastases; in the same manner he states that a primary sarcoma of the tibia can give rise to a similar lesion. Ewing also cites a case described by Vogel where by way of a retrograde lymphatic path renal metastases arose from cancer of the gall bladder.

Two other cases are cited, both reported by Zahn, where metastatic growths were found in the kidney, one from sarcoma of the seminal vesicles, the other from cancer of the thyroid, both apparently being due to the presence of a patent foramen ovale, the so-called "paradoxic embolism" already referred to.

We have spoken already of a case reported by Böger. In this instance there was a primary cancer of the rectum with metastases to the pelvic ureter and to the kidney on the left side. The ureteral growth occluded its lumen, giving rise to a considerable degree of hydronephrosis. The lesions in the kidney replaced two or three of the pyramids in the lower pole. In view of the fact that no evidence of tumor cells could be found in the blood vessels or lymphatics of the ureter, Böger concluded that the kidney lesions were in the nature of implants from cells being carried into the kidney from the growth below it in the ureter.

Lubarsch is quoted by Böger as having reported 2 per cent of kidney metastases in a series of 850 cases of cancer of the rectum.

Walter has reported a very interesting and unusual case of metastatic cancer of the uterus in a kidney already the seat of hypernephroma. Microscopic examination showed capillaries and arteries in the midst of the hypernephroma filled with cancer cells. This author refers to a case described by Bormann, wherein squamous-cell carcinoma, primary in the uterus, gave rise to metastases in the kidneys as well as in many other organs.

Mariconda records a case of diffuse melanosarcoma with metastases in the renal glomeruli. In an exhaustive monograph of primary cancer of the lung, Fried mentions six cases of mestastases to the kidney, one of them bilateral. He states that Kikuth, in a series of 240 cases of cancer, found the following distribution of metastases: liver, 70; bones, 48; lungs, 43; brain, 31; kidney, 25; suprarenals, 21; pancreas, 11; thyroid, 5; cardiac muscle, 4; intestines, 3; stomach, 2; spleen, 2; gall bladder, 1; ovary, 1.

In a personal communication to one of the writers, Shields War-

ren states that he has found fifty-two instances of metastases to the kidney in "a little over 1,000 cases of malignancy."

Taking all the cases of metastatic malignancy of the kidney reported in the form either of case reports or of statistics we find 107 instances. While no claim is made that the literature may not yield additional numbers, we believe that the figures we present are sufficient to show the relative infrequency of the lesion. This comparative paucity of material may well be due to the fact, as we shall show later, that no case, as far as we know, has developed clinical signs or symptoms.

This seems to us to demonstrate quite clearly that metastases to the kidney are a late phenomenon, so late, in fact, that before they can develop to a sufficient degree to attract the attention of the clinician, the patient is overwhelmed either by his primary tumor or by its metastases to other parts of the body. It seems unreasonable to suppose that, given the time and opportunity, metastases will not develop in the kidney under circumstances quite as favorable as those existing in other organs.

With the object of adding to our knowledge of the subject under discussion a careful study was made of the autopsy records at the Massachusetts General Hospital. A total of 6,700 records has been perused, of which 1,116 were of those dying with malignant disease.

It has been interesting in our study of these 1,116 autopsies to find that in nearly 50 per cent the primary growth was in the gastro-intestinal tract, the genito-urinary tract coming next with about 18 per cent of cases. In round numbers this represents 468 cases of gastro-intestinal malignancy, and 220 involving the male and female genito-urinary organs.

On the other hand, these figures are misleading as is shown by a more detailed study. There was altogether a total of forty instances of renal metastases, this being 3.5 per cent in the total of 1,116. It would appear, therefore, that renal metastases are relatively uncommon, a finding which agrees with the statement by Warren, already referred to. Detailed analysis of these metastases shows interesting features, these being shown in the accompanying chart (Fig. 1). The 100 per cent occurrence of metastases in neuroblastoma and various types and locations of sarcoma is impressive, but it must be remembered that only one, two, or three

instances of these lesions were encountered. The same is almost as true of the four cases of thyroid malignancy with renal metastases in 50 per cent. It so happens that sarcoma was the type of neoplasm in all these cases so that taken as a whole the likelihood not only of metastases, but of renal metastases in various kinds of sarcoma, is extremely great.

Type and Location	Number Cases	Number Metas.	Per Cent
Melanotic Sarcoma	3	3	100
Neuroblastoma	1	1	100
Sarcoma	2	2	100
Thyroid	4	2	50
Lung	20	6	30
Pleura	7	2	28.5
Undetermined	18	4	22.2
Liver	20	3	15
Testis	7	1	14.2
Adrenal	7	1	14.2
Breast	26	3	11.5
Esophagus	52	4	7.6
Pancreas	76	2	2.6
Bladder	48	1	2.08
Gastro-intestinal	468	5	1.06

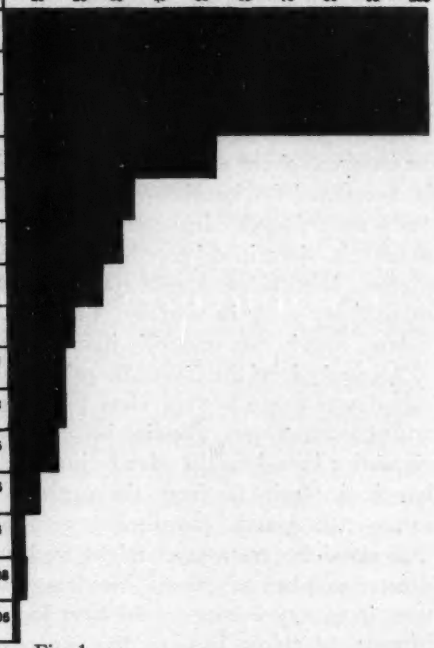

Fig. 1

Coming now to the neoplasms of various other organs we find that those of the lung are far in the lead in the production of renal metastases, with those of the pleura a close second. It interested us greatly to note that no case of prostatic cancer gave rise to metastatic growths of the kidney, even though the lymphatics of the prostate generally drain into those receiving drainage from the kidney. More striking, however, is the fact that in forty-eight

cases of bladder tumor, metastases reached the kidney in but one instance. Here, if anywhere, one would believe that the conditions were ideal for metastatic growth, either by the lymphatics or, perhaps, by way of the lumen of the ureter itself. The circumstance may be explained partly by the relative infrequency with which bladder neoplasms form metastases. As a final observation it seems extraordinary that out of 468 neoplasms of the gastro-intestinal tract they metastasized to the kidney in only 1.06 per cent of cases. No explanation is offered for this interesting phenomenon.

We have said that in none of the cases of metastatic malignant disease of the kidney, found at autopsy, was there any evidence of symptoms or signs in the clinical record. It is true that in many albumin, pus or blood, singly or in combination, were found, but in no case was there any excess of these elements or more than could be accounted for in other ways. In many kidneys, multiple metastases were found. In some, these growths were but a few millimeters in size; in others they measured from 1 to 3 centimeters across. Both kidneys were found to bear metastases in twenty-five, or 62.5 per cent; in fourteen, the kidney on only one side was involved, and in one case this item was not recorded.

An analysis of the forty autopsies in which renal metastases were found was made with a view to determining what other organs and structures were likewise involved. In twenty-seven there was glandular invasion, the glands involved being those receiving the lymphatic drainage from the organ primarily concerned, but in many cases glands far distant were likewise invaded. We feel that glandular metastases might well have been recorded in a far greater number of cases. The lungs were found to bear metastases in twenty-five cases; the liver in twenty-three; the adrenals in fifteen; the spleen in nine; the pancreas and brain in seven each; the heart, stomach, pleura and peritoneum in five; the esophagus, small intestine, pericardium, vertebræ, mesentery and mediastinum in three; the gall bladder, ovary and pituitary gland in two; and the "neck," dura, diaphragm, bronchial glands, skin, uterus, optic nerve, piarachnoid, testicle, large intestine, abdominal wall, omentum, cecum and appendix in one each. Other bones than those of the spine were involved in eight instances, namely femur, ribs and skull in two each, and the tibia and sternum each in one case.

It is thus obvious that the kidney was only one of the many regions to which metastatic growths traveled.

We do not attempt to explain the very marked tendency of cancer of the lung and pleura to metastasize to the kidney (this being 30 per cent and 28.5 per cent, respectively). Certain known facts, however, are of help. As Fried says, "Primary cancer of the lung possesses vigorous metastatic power and its metastases are, as a rule, widespread." This fact, however, is not really any explanation at all—it seems to be only a fact. On the other hand, the circumstances may be explained on an anatomic basis, which is that whereas cells breaking from the lung can easily enter the general circulation, those coming from elsewhere in the body must first pass through the sieve of the lungs. Here, again, we find ourselves facing a paradox, for on this basis why would not the lungs be analogous to a trap for any stray malignant cells coming from other organs or structures? Yet this does not seem to be the case. In other words, we cannot explain our findings. All we know is that the cells of malignancy find their way to distant parts in a variety of ways, and we are in accord with Fried, who says, "At the present time there is general agreement that cancer metastasizes to distant organs by way of every possible channel."

From this study of our own material and from that reported in the literature, we are forced to the conclusion that metastatic renal malignancy is relatively uncommon; that it is most likely to occur in the course of primary cancer of the lungs and pleura; that no evidence is at hand to show that it produces clinical signs or symptoms; that no adequate explanation can be given for the observations; and finally, that Virchow's statement that "organs frequently originating cancers are rarely the seat of metastatic cancer," may be applicable to the subject of this discussion.

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DISCUSSION

Dr. Edward L. Keyes (New York City): Does Dr. Lower really think that the endocrine function of the testicle is not interfered with in cryptorchidism? Surely clinical observation suggests that after reduction of testicles into the scrotum, the patient's eunuchoid characteristics seemed to disappear or be materially changed without any endocrine attempt to influence them.

I am very interested in Dr. Lower's conscientious investigation of testicular function. One might infer, not altogether seriously, from his observations that the human race is made up of not entirely normal rats.

Dr. William E. Lower (Cleveland, Ohio): We have made some check on these cases of cryptorchidism and have found that the amount of sex hormones seemed to be just as great as in normal cases. We have taken blood and urine from these patients and have injected them into capons with practically the same amount of comb growth as was obtained from patients whose testicles were in the scrotum.

The same thing happens in the lower animals. In animals in which the testicles are placed up in the abdomen, experimentally, we have noticed no change in the secondary sex organs.

Histologically, the number of interstitial cells is not reduced as a result of the interference with the tubular part of the testicle, and that has recently been shown in a rather large series of investigations of histologic specimens in which it was found that the interstitial portion has a tendency to increase rather than to decrease. That is, if there is interference with the tubular part of the testicle either by x-ray—and that part of the testicle is rather sensitive to x-ray—or by some other factor, there is an increase in the number of interstitial cells. With that as a theory, we believe what, perhaps, would take place would be that as the tubular part goes out of commission, the hypophysis gets larger and this increases the activity of the interstitial cells. This may be a factor in the production of the prostatic hypertrophy.

CYSTINURIA AND CYSTIN STONES

FURTHER OBSERVATION OF THIS CONDITION WITH A REPORT OF THREE NEW CASES

HERMAN L. KRETSCHMER, M.D.
Chicago, Illinois

The subject of cystinuria and cystin stones constitutes a very interesting chapter on urinary calculi for the following reasons: First, because of the relatively infrequent occurrence of cystin stones: second, because many authors are of the opinion that this type of stone represents a different entity, that is, they believe that this entity is due to a disturbance of metabolism, and third, because of some difference of opinion regarding the relationship between cystinuria and cystin stone.

During the past fifteen years a renewed interest in this subject has taken place, if one may judge by the large number of papers that have been published.

In 1916, I reported two cases (in twin brothers) of cystinuria complicated by cystin stones. The paper included a review of the relevant literature to that date.

In the present paper, three cases, which have occurred in my practice since the earlier publication, are reported, along with a brief survey of the literature on cystinuria and cystin stones since 1916.

Case 1.—C. C., male, aged twelve years, was admitted to the Children's Memorial Hospital, November 9, 1932, on the service of Dr. Kraft.

History.—At the age of four months, the infant entered the hospital because of difficulty and pain on urination for which a circumsion was done. Two months later he developed an otitis media and mastoiditis, necessitating a mastoidectomy. Between the ages of five and ten years, he had chicken pox, measles, whooping cough and mumps. Family history was negative for stones.

Present Complaints.—The patient was admitted to the hospital with right-sided abdominal pain, anorexia, vomiting and fever. He was apparently in good health until forty-eight hours previously when he awoke complaining of abdominal pain. He ate no breakfast and about three hours later began to vomit. He vomited several times

during the day; the pain on the right side was continuous, but he was up and about. That evening his mother gave him a teaspoonful of castor oil. He slept all night and felt well in the morning, ate breakfast and dinner, and during the morning had two watery bowel movements which were accompanied by pain on the right side. Twenty-

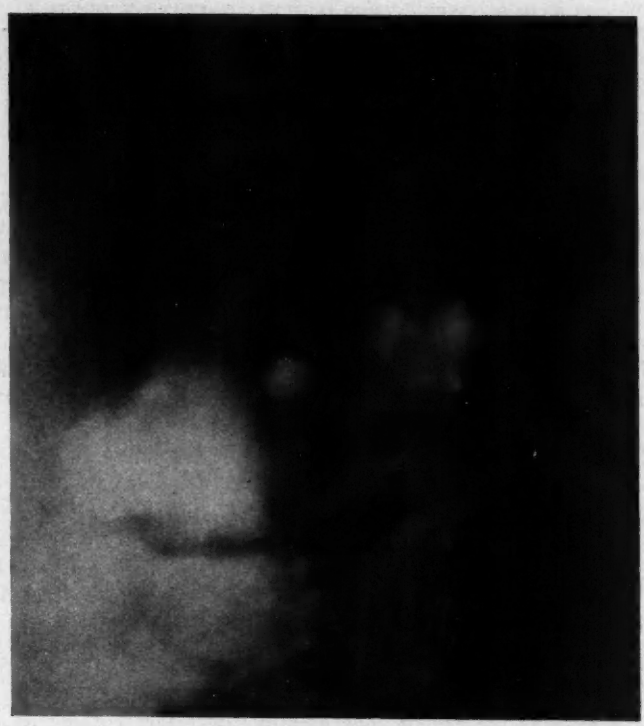


Fig. 1. Case 1. Roentgenogram showing two stones in region of the right kidney pelvis.

four hours ago the pain recurred and kept him awake. He vomited once. Today the pain is almost continually present; he is unable to eat, and has vomited four times. His mother believes he has had a slight fever for the past twelve hours.

Physical Examination.—The patient was a rather pale, well-developed and well-nourished boy, who did not appear acutely ill. Examination of the head and neck was negative. Heart and lungs

were normal. A generalized rigidity, of moderate degree, was found over the entire abdomen, but especially over the upper right quadrant. There was tenderness over the entire right side, and a point of *severe* tenderness 1.5 cm. above McBurney's point. Deep palpation on the left side caused pain in the upper right quadrant.

The impression gained from the history and physical examination was that the child had an acute appendicitis until examination of the urine was made, which showed: Albumin +, Acetone ++, benzi-

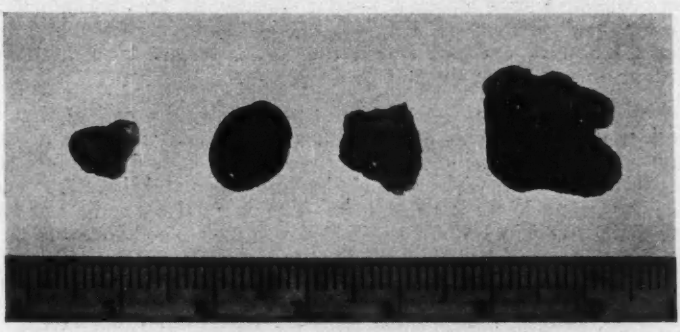


Fig. 2. Case 1. Stones removed at operation.

dine ++, ten to twelve red blood cells per high power field, an occasional leukcoyte, numerous cystin crystals, and no casts, no bacteria in stained specimen.

Blood Examination.—Leukocytes 19,650, polymorphonuclears 84 per cent, and lymphocytes 11 per cent.

Von Pirquet test was negative.

Roentgen-ray Examination.—Two stones were found in the region of the right kidney pelvis (Fig. 1).

Intravenous Pyelogram.—There was a slight delay in visualization of the dye on the right side and a slight dilatation of the pelvis and ureter. A normal kidney and ureter on the left side, and increased density of the shadows in the region of the right kidney stones.

Operation was performed November 25, 1932 (ether anesthesia). The upper third of the kidney, which was resected, showed a large cavity with a narrow outlet. The stones were found in this cavity (Fig. 2).

Postoperative Course.—The patient made an uneventful recovery. Subsequent examinations of the urine during his stay in the hospital showed no cystin. He was discharged December 12, 1932.

Chemical examination of the stone showed it to be pure cystin.

Examination of the urine on April 27, 1933, showed cystin crystals and the chemical test for cystin was positive.

Case 2.—Mrs. R. P., female, aged twenty-eight years, was admitted to the Presbyterian Hospital, March 11, 1933.

History.—At thirteen years of age the patient had inflammatory rheumatism which lasted one month. Seven years ago, pain in the back was diagnosed as "sacro-iliac dislocation." This was treated by an osteopath and cured. Sacral backache has been present for many years following exertion and during pre-menstrual period. Family history was negative for stones.

Present Complaints.—Two weeks previously, the patient first experienced a dull, aching sensation in the abdomen and back, a condition which gradually increased in severity until four days before coming to the hospital, when the pain became sharp and there was knife-like pain in the lower left quadrant. The pain did not radiate and was relieved by codein. The patient began to pass blood in the urine at the same time and had been confined to bed since, with no recurrence of sharp pain, although the dull, aching pain in the back had been more severe and became localized in the left lumbar region. The condition remained unchanged until the patient motored to Chicago the morning of March 11, during which time she again had severe knife-like pain in the lower left quadrant associated this time with nausea and vomiting. There had been no frequency, urgency, retention or dysuria, and no pain in the lower right side.

Physical Examination.—The patient was a well-developed and well-nourished woman suffering from severe pain. Examination of the head, neck, heart and lungs, was negative. There was an area of tenderness over the course of the ureter.

Blood Examination.—Red blood cells 4,600,000; white blood cells, 15,100; hemoglobin 82 per cent. Blood pressure was: Systolic 138; diastolic 90. Blood chemistry showed creatinine 1.3, non-protein nitrogen 33.7.

Phenolsulphonephthalein test gave the time of appearance of dye, fifteen minutes; total output for one hour, 55 per cent.

Urinalysis.—There was no sugar; albumin, trace; blood +; leukocytes 10 per c.m.; red blood cells 180 per cubic millimeter; cystin crystals. Culture of the bladder urine was sterile.

Roentgen-ray Examination.—Kidney outlines were of normal size and position. There was a small area of increased density between the transverse processes of the first and second lumbar vertebræ on the left side (Fig. 3).

Intravenous Pyelogram.—The density in the left kidney was markedly increased by the dye, but the pelvis was not visualized; however, there was some media in the region of the increased density which is probably in the upper ureter. The pyelogram on the right side was normal.

Fig. 3. Case 2. Roentgenogram showing a small area of increased density between the transverse processes of the first and second lumbar vertebræ on the left side.

Operation was performed March 13, 1933 (ethylene anesthesia). The usual oblique lumbar incision was made on the left side. The kidney was freed and the stone was felt at the uretero-pelvic junction. An incision was made in the pelvis exposing the top of the stone (size of a lima bean) which was wedged in the ureter. The stone was removed, a rubber drain tube inserted into the kidney pelvis and sutured with catgut.

Postoperative Course.—The patient made an uneventful recovery, and was discharged April 4, 1933.

Following the removal of the stone, the cystin crystals disappeared from the urine, but chemical tests for cystin were positive until the patient left the hospital.

Chemical examination of the stone showed the hard center (size of a pea) was composed of calcium phosphate. The remainder of the stone (size of a lima bean) was yellow and consisted of cystin and uric acid.

Examination of the urine on April 18, 1933, was negative for cystin crystals, and chemical test was negative for cystin.

Case 3.—L. M., female, aged twenty-two years, was admitted to the Presbyterian Hospital, February 22, 1930.

History.—The patient had the usual childhood diseases including diphtheria and scarlet fever. At seventeen years of age she had colitis. About a year ago, having previously felt well, she had a sudden, intense pain in the left mid-axillary line just above the ilium which caused her to vomit. The pain left abruptly after about twenty minutes, but was succeeded by a rhythmical ache which lasted about two to three days, when a *stone was passed*, followed by some soreness for a day or two. A second attack occurred one month ago, and under the same circumstances the patient *passed another stone*. Both stones were recovered in the urine. Between the two attacks the patient had occasional pain in the same region. Frequency of urination (eight to ten times per day) had been present as long as she can remember. Occasionally there had been slight burning on urination, and at intervals a dull ache across the back at the level of the upper lumbar vertebræ.

The patient states that her mother had frequency all her life and had "bladder" trouble during both pregnancies.

Physical Examination.—The patient was a well-nourished and well-developed white female who did not appear ill. Examination of the head was negative. There was one small hard lymph gland in the right anterior cervical triangle of the neck. Examination of the heart and lungs was negative, as was that of the abdomen, except for costovertebral tenderness on the left side.

Blood Examination.—Red cells 5,150,000, white cells 8,500, hemoglobin 98 per cent.

Blood pressure was: Systolic 118, diastolic 74.
Blood Wassermann and Kahn's tests gave negative results.

Urinalysis.—There was no sugar; albumin 0; blood 0; cystin crystals ++; occasional pus cells.

Cystoscopic Examination.—The bladder was normal. Ureters were catheterized without difficulty or obstruction. The urine obtained from the bladder, right and left kidneys was free of pus and sterile on culture.

Roentgen-ray Examination.—The kidney outlines were of normal size and position. There was no evidence of stone.
Pyelograms.—Right and left kidneys were within normal limits.
Chemical examination of stone which was passed showed it to be cystin and uric acid.
Examination of the urine on April 11, 1933, showed cystin crystals.

One of the significant advances in the study of cystinuria has been the perfection of practical laboratory tests for the chemical demonstration of cystin in the urine in more than normal amounts. Formerly the clinical diagnosis of cystinuria was dependent on the demonstration of the characteristic crystals in the urine. The recent chemical tests of Sullivan and of Brand and his co-workers furnish a much more accurate method of diagnosis and have shown that cystinuria may exist where the crystals do not appear in the urine.

Probably more cases of cystinuria, as well as cystin stones, would be recognized if these tests were used routinely in all cases of urinary calculi or in patients suspected of having urinary calculi.

Failure to demonstrate cystin crystals is not an adequate criterion of the absence of cystin. In case 2 the surgical removal of the stone was promptly followed by a disappearance of the cystin crystals from the urine, yet chemical tests were positive for cystin during the patient's stay in the hospital.

HISTORICAL DATA

Wollaston (1810) described a new type of urinary calculus, two specimens of which he had studied. Since they were both bladder stones, he termed the substance of which they were composed "cystic oxide."

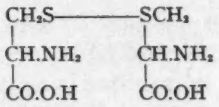
Berzelius (1833) suggested the change of the name from "cystic oxide" to "cystin," and on this change Civiale commented, in 1838,

that while it corrected an error in chemistry, it perpetrated an error in physiology, as cystin is excreted by the kidneys and does not originate in the bladder.

The sediments of hexagonal crystals found in the urine, upon which the diagnosis of cystinuria is most frequently based, were first observed by Stromeyer in 1824, and by Pront. Pront made the earliest analysis of cystin, but this was inaccurate as he reckoned the sulphur content as oxygen.

Baudrimont and Malaguti announced that cystin contained sulphur, and Thaulow published a complete analysis of the compound.

The establishment of the true formula of cystin has been established by such men as Goldmann and Baumann and Erlenmeyer.



The existence of an isomer of cystin was prepared synthetically by Gabriel in 1905.

Garrod states that there is some discussion in the literature of the fact that some cystinuric patients excrete this iso-cystin (the isomer of ordinary cystin). He concludes from his own studies and the evidence of others that "it is obvious that the occurrence of iso-cystin as a metabolic product is as yet very far from proven."

Garrod mentions the various cases in the literature in which diamines, cadaverin, putrescin, et cetera, have been found in the urine of cystinuric patients. While not uniformly found by any means, Garrod feels that it is significant that "such searches for diamines have invariably proved fruitless save in cases of cystinuria."

THE INFLUENCE OF HEREDITY

The hereditary tendency of cystinuria is a well-established fact. In many of the cases reported in the recent literature, examination of the patient's family has revealed cystinuria in a considerable proportion of the other members.

In my two previously reported cases, many members of the family showed cystin. Of the six members of this family (excluding the father who would not send in a specimen of urine)

two had cystin stones, two showed the presence of cystin crystals, one showed the presence of a sulphur reaction, and the sixth was normal.

In the three cases reported in this paper the following was noted with respect to the occurrence of cystinuria in other members of the family:

In Case 1, of the two other members of the family whose urine was examined, one showed the presence of cystin crystals and one was normal. In Case 2, two of the other members of the family showed a positive chemical test for cystin. In Case 3 no specimens of urine of other members of the family were sent in for examination.

The most extensive and instructive study of a cystinuric family was that published by Thin, in 1929. Because of the detailed study that was given his cases, it might be desirable to mention the results of this study in detail. It concerns the history of the offspring of two half-brothers who married and had large families. The medical histories of these two half-brothers, traced through several generations, showed no evidence of gross calculous disease.

History of the Family of the Older Half-Brother.—The older of the two half-brothers lived to old age and was a dyspeptic. His wife was gouty and arteriosclerotic. Repeated examinations of their urine gave no evidence of cystinuria. This couple had twelve children, seven of whom showed cystinuria as they came to adolescence.

The third child, female, had a litholapaxy performed three times between the ages of twenty-seven and forty-five, and has been free from symptoms for eleven years.

The fifth child, also female, had a right-sided renal colic at the age of seventeen, and frequently passed small cystin calculi. Later, removal of her right kidney and ureter was necessitated by calculous disease, and death resulted from urinary complications.

The sixth child, male, had never shown cystinuria, but a son of his developed this condition at the age of fifteen.

The seventh child, female, had renal colic prior to her marriage, and died following an operation for removal of a cystin calculus from the pelvis of the left kidney. This woman was the mother of five children, four of whom developed cystinuria at adolescence. Her eldest daughter at twenty-six had an attack of renal colic and

passed cystin crystals. Her eldest boy, at the age of twenty-three, developed left-sided renal colic and was operated upon for an impacted cystin calculus in the left ureter. Two other sons showed cystinuria but no colic or evidence of calculus formation.

The eighth child, male, showed cystinuria, but developed no complications.

The tenth child, male, showed cystinuria, but developed no complications. He had a son who showed cystinuria.

The eleventh child, male, had frequent attacks of colic since early youth. He was operated upon for calculus anuria due to calculi in both kidneys and ureters. About ten years later he died with urenic symptoms.

The twelfth child, male, has had nine litholapaxies for cystin stones.

History of the Family of the Younger Half-Brother.—The younger half-brother had ten children, none of whom had cystinuria. Three of these married their cousins belonging to the family of the older half-brother (Nos. 6, 7 and 11). The progeny in two cases were afflicted with cystinuria, and in the third case the offspring has not yet arrived at the age when cystinuria has the habit of appearing.

Another daughter of the younger half-brother married a more distant relative and has a son, seventeen years old, who developed a small cystinuric renal calculus which became impacted in the ureter and was removed surgically. Five other members of this family did not show cystinuria.

The author observed that apart from cystinuria and the complications arising from it, these people are unusually healthy and vigorous, and not neurotic as some authors have claimed.

INCIDENCE

In 1916, I was able to gather a series of 107 cases of cystin stones (including in this number the two cases which I reported at that time) since the first report of such a case by Wollaston, 115 years previously.

Lewis (1932) stated that in a search of the literature over a period from 1921 he found seventy-one cases of cystinuria, calculus formation not being observed in all.

Simon encountered only one example of cystin sediment in the examination of 15,000 urines and Primaoma found one in 20,000.

Lewis, by means of the Brand and Sullivan tests, found twenty-nine positive cases in 11,000 healthy young men and women, a very much higher percentage of positive cases than had been obtained by any other investigator, so far as I know.

These findings led Lewis to conclude that there seems little doubt that cystinuria in the sense of the excretion of abnormal amounts of the amino-acid in the urine, may be of more common occurrence than is to be inferred from the reports of the finding of cystin calculi or cystin crystals in the urine.

Eppinger stated that the usual conception that about 2.5 per cent of cystinuric individuals develop stone is probably putting the figure too high, since large numbers of cases of cystinuria are never recognized.

Nakano found seven instances of cystin stones in 600 cases of urinary calculi.

Although generally admitted as being a rare clinical entity, not all authors share this belief. Thus, Seeger and Kearns feel that cystinuria is not so rare as statistics would indicate, since a considerable number of cases are symptomless and are, therefore, overlooked, and even when complicated by stones are not always recognized. These authors say that the appearance of the stone may be disguised because of a mixture of other deposits and, again, resemblance of the stones to the common triple phosphate concretions may be confusing.

ETIOLOGY

It can probably be stated without fear of contradiction, when we say that the cause of this exceedingly interesting condition is unknown. Much investigation has been carried out, yet no satisfactory explanation has been found.

Robson found that in his case neither the amino-acids, tyrosin and leucin, nor the diamins, putrescin and cadaverin, could be detected in the urine of his subject which supports the idea that in the cystinuric patient the derangement in protein metabolism is limited strictly to excretion of abnormal quantities of cystin. This author carried out feeding experiments with the isolated amino-acid cystin which showed that this compound ingested is oxidized to inorganic sulphur compounds, thus confirming the work of other

writers in the conclusion that the cystinuric patient oxidizes cystin, fed as such by mouth, in a normal manner.

Robson contends that the fact that the peak of the curve of the patient to oxidize cystin had not been reached when as much as 8 grams of cystin per day were administered, would tend to refute the suggestion of Hunter and Eagles that "one of the errors in cystinuria lies in the incapacity of the liver to handle the cystin normally in reserve there."

Robson feels that the fact that the cystinuric patient can oxidize large amounts of cystin administered orally, together with the fact that the quantity of urinary cystin, according to his experience varies directly with the amount of protein fed, would make it appear that "the error is not one connected either with the normal process of oxidation or with the organ in which that process takes place."

He concludes that the disturbance is closely related either to the digestive processes of the organism, or to the permeability of the intestinal wall. The fact that cystin fed as such is completely oxidized, while some of the cystin arising from dietary protein escapes oxidation, would suggest that the amino-acid in the latter case is actually passing from the intestines into the portal system, not in the free form, as it does normally, but as a peptid, and as such escapes the normal oxidation processes in the liver. Fission of this peptid might result when it reached the tissues and encountered the intracellular enzymes. Cystin would then be liberated only to be excreted by the kidney owing to its presence in abnormal amounts in the blood stream.

Robson notes that this theory receives support from the fact that Blum (1903) found that experimental cystinuria could be produced by injection of cystin into the peripheral circulation. Such facts would be met if, in the cystinuric patient, the passage through the liver was effected by the cystin in the form of a peptid, in which it was so linked up that it escaped the normal processes of deamination and oxidation.

Robson says, "A possible solution of the problem of metabolism presented by the cystinuric patient lies in the feeding of complex peptids containing cystin, and it is probable that a more exact knowledge of the action of enzymes on the protein molecule might

give clearer indication of the source of the urinary cystin in this type of condition."

CLINICAL SIGNIFICANCE

It is usually considered that, except for the complications attendant upon cystin calculus formation, cystinuria is a harmless anomaly, since it is a well-recognized clinical fact that many individuals have cystinuria for many years or for a lifetime and never develop calculi, while others develop calculus disease. It is when calculus disease develops that cystinuria becomes of clinical importance.

Umber notes that cystinuric patients may be symptomless all during life. He is of the opinion that in case there is a special tendency to stone formation, or a co-existing disturbance of the colloidal elements of the urine, pure cystin stones may form, or a calculus may result by a secondary deposit of urinary salts on a cystin nucleus.

In Case 2 reported in this paper the reverse was true, namely, the nucleus of the stone was composed of calcium phosphate. This was surrounded by a deposit of uric acid, and this in turn was covered by a deposit of cystin.

It has been noted by several authors that cystin calculi are less likely to be associated with infection then is the general rule. In the three cases that form the basis of this paper, all patients had a sterile urine.

Because of the oft-repeated statement that cystinuria is a relatively harmless condition, it might be well to point out that there is evidence which suggests, however, that disturbance of cystin metabolism in young children may at least prove to be of serious consequences. In a case reported by Abderhalden, a cystinuric child who died with symptoms of general failure of nutrition, showed cystin deposits in the tissue, particularly the liver. Two other children in this family had died with similar clinical symptoms. Lignac made similar observations on three young children who were not related. These children had shown inanition, and a progressive general atrophy, with fatal outcome. At autopsy cystin crystals were demonstrated in many organs (spleen, liver, choroid plexus, mesenteric lymph-nodes, and so forth). These crystals were demonstrated by microscopic and chemical methods.

In view of the fact that cystin is believed to be an essential amino-acid, in the absence of which growth and normal nutrition are impossible, as has been demonstrated in the white rat, Lewis concludes that these autopsy findings suggest that lack of normal utilization of cystin in those children may have been responsible for failure of normal growth and nutrition which terminated fatally. It is possible, says Lewis, that, in older patients, requirements for cystin are not as great as in growing individuals and that cystinuria in adults does not result in as serious a disturbance of the metabolic processes. He states that the frequent reference to "gouty attacks" and rheumatism in the clinical reports of cystinuric patients suggest that cystin may be commonly deposited in the tissues of cystinuric individuals in the manner reported by Abderhalden and Lignac.

Looney, Bergland and Graves state that there is no satisfactory explanation as to why one cystinuric patient develops calculi and another does not. They state that the element of infection is not seemingly important, according to their experience, since one of their patients showed persistent formation of stones with no sign of infection, while another, with heavily infected urine gave no history of calculi.

QUESTION OF OPACITY OF CYSTIN STONES TO X-RAY

The question of the visibility of the cystin calculus to Roentgen rays is still a far from settled one. Thus, Holmes and Ruggles state that the order of visibility of urinary stones is as follows: Phosphate and cystin very dense, oxalates next, and urates least. Mecalpine reports a case where good x-ray shadows were obtained of six cystin stones in the kidney of a boy eight years of age. Beer concludes that the x-ray would seem to show large, but not small cystin stones. Harris states that the older literature which asserts that cystin stones are not opaque, is erroneous, and according to Lewis the general opinion seems to classify them as shadow-casting (often faint). Thomas and Roda are also of the opinion that cystin stones may cast a very distinct shadow.

Ewell as well as Culligan, state that calculi which do not cast a shadow are usually composed of pure cystin, xanthin or uric acid. In Graves' case repeated x-ray studies failed to demonstrate the stone.

Hicks says that small cystin stones are only slightly, or not at

all, opaque to x-rays and consequently this means of diagnosis is not very important in their detection.

It would seem, therefore, that in patients with a history of renal colic, who show the presence of cystin crystals in the urine, or who give a positive test (Brand or Sullivan tests) for cystin, and in whom the x-ray is negative, repeated examination with the wax-tipped catheter is in order.

TREATMENT

The treatment of cystin stones does not differ from that of any other type of stone in the urinary tract, and most authors agree that the treatment is surgical. Stones in the kidney pelvis are the best removed by means of a pyelotomy (with drainage through the lower pole as was done in Case 2). Stone in the ureter can be treated either with dilatations and injections of sterile oil or by an extraperitoneal ureterotomy, and bladder stones can be easily handled by means of the lithotrite.

For a long time it has been known that cystin is soluble in an alkaline solution and the administration of alkalies is recommended not only to cause disintegration of a stone when present, but to prevent the formation of stones in cystinuric people or to prevent their recurrence after they have been operated upon. Among the early writers to advise the internal administration of alkalies must be mentioned Cantani and Beale, who advised large doses of carbonate of ammonia, and Klemperer and Jacoby, who recorded remarkable results with the alkaline treatment.

Because of the tendency of this type of stone to recur, the value of the surgical treatment has been questioned and attempts have been made to produce disintegration of the stone by the internal administration of alkalies. Cases of successful termination by the internal administration of alkalies were recently reported by Reeves and Crowell, although the latter, in addition to the internal administration of alkalies, irrigated the renal pelvis with an alkaline solution.

The necessity for a diet low in protein has been stressed by many writers for a long time. Robson concludes from his studies that the only safe method of treatment of the cystinuric person is cutting down the dietary protein as far as it is compatible with the maintenance of dietary nitrogen equilibrium and, furthermore, the

results from the continued use of sodium bicarbonate, as suggested by some authors for the purpose of rendering the urine alkaline, are not conclusive.

Steinitz and Remen, however, specify the necessity of a diet low in the mother substance of cystin, as the essential in the treatment of cystinuria.

Although many clinicians believe that regulation of the diet and the administration of alkalies should be employed in every case of cystinuria, Hicks says no treatment for cystinuria is indicated unless calculi are manifested. Protein reduction in the diet and sodium bicarbonate by mouth may then be tried. He further states that surgery may be employed for an obstructing calculus, but it may prove disappointing due to the tendency for such stones to recur.

On the other hand, many years may elapse between the removal of a stone and a recurrence, even though no attempt has been made to prevent such recurrence either by the internal administration of alkalies, the regulation of the diet, or both.

CHEMICAL COMPOSITION OF CYSTIN STONES

Cystin may be the sole component, or there may be varying amounts of phosphates, and if the latter are present to any marked degree there is usually some carbonate present. Nakano made a careful study of seven cystin stones which he found in a series of 600 urinary stones. The following is taken from a table in which the typical quantitative analysis of various types of stones, diagnosed as cystin, showed:

Cystin	P_2O_5	Na	K	Ca	H_2O	Total N
80.10	1.30	2.80	0.10	1.02	2.26	10.73

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A SIMPLE METHOD OF CHEMICAL ANALYSIS OF URINARY CALCULI

REPORT OF THE CHEMICAL COMPOSITION OF A RECENT SERIES

ALEXANDER RANDALL, M.D., and (by invitation) HAROLD G. BEESON, M.D.

From the Department of Urology, University of Pennsylvania

It is an old and well founded law of logic that similar causes are apt to produce similar effects, and when one applies the converse of this to the story of calculus formation in the urinary tract, the logical answer becomes: The cause of stone must vary, for the effect is known to be a variant. It is hard to conceive, by any stretch of chemical or physiologic imagination, that the same causative factor, or factors, which create the formation of a uric acid stone in an acid urine can be the same as the causative factor, or factors, which give rise to a stellate phosphate, or a calcium carbonate stone in an alkaline urine. For these reasons it seemed necessary, when starting some investigative work aimed towards an elucidation of the cause of urinary calculus, that the first step should be an analysis of the stones as found and an immediate separation of the problem into component groups of cases whose differentiation was based on the chemical constituents of the stone as found. This necessitated the finding of a simple form of chemical analysis for such a study and it was rather startling to discover that current urologic literature did not take into consideration this simple subject in the studies on stone. This criticism can be held against all current text-books, and even the few monographic studies of recent date beg the question entirely. In the modern urologic literature one is quite overwhelmed by the vividness with which plausible theories on etiology are defended, each being rather consistently held to explain the cause, or made to cover the etiology, of all varieties of urinary calculi and the limit seemed to be reached in a recent research article where stone was actually produced in animals under certain experimental conditions, though actually in the extensive report of the same, the chemical character of the calculi so produced is unrecorded.

I am of the opinion that there will be found a fundamental simple

single cause, as yet undetermined, to account for stone formation and that secondary factors will then enter to vary the actual chemical composition in individual cases. As none of the present day theories answers the question of etiology in its entirety, they must all belong to the group of secondary factors.

Perhaps it could be truly said that extensive and competent studies on the chemical composition of stone have been performed in the past to no avail; nevertheless, it is a striking fact that the chemistry of calculi has varied markedly in different countries and at different times, and today this knowledge of their chemical character has not yet been correlated with our modern knowledge and

KIDNEY CALCULI—THIRTY-FOUR CASES

	Cases	Per cent	Pure	Per cent
Calcium-magesium phosphate	12	35.3	7	58.0
Calcium oxalate	11	32.3	9	81.8
Calcium carbonate	10	25.9	3	30.0
Uric acid	4	11.7	2	50.0
Triple phosphate	4	11.7	1	25.0
Mixed	11	32.3	0	00.0
Sodium ureate	3	8.8	0	00.0
Fibrin	2	5.8	0	00.0
Urostealith	1	2.9	1	100.0

concept of metabolic diseases, dietary deficiencies, focal infections and endocrine dysfunctions, nor has it been correlated with our modern methods of quantitative chemical analyses of blood and urine.

It is for these reasons, offered as an apology, that I bring forward a simple method of qualitative chemical stone analysis originally formulated by Olof Hammarsten and published by him in 1890, in the second German edition of his book, an authorized American translation of which was made by J. A. Mandel in 1893. Hammarsten's original outline has been modified and changed in certain steps by one of my co-workers, Dr. J. S. P. Beck.

This analysis can be performed by any intelligent laboratory technician with a minimal amount of laboratory equipment. The amount of stone necessary for a complete analysis would rarely

exceed 50 milligrams, and the amount of time required averages approximately fifteen minutes. The calculous material is run through a simple series of inorganic chemical analytical steps, where, by the process of exclusion, one gets to a final conclusive diagnosis.

During the past eighteen months we have had the opportunity of studying 117 cases of urinary calculus, and at this time I wish to

URETERAL CALCULI—FIFTY-TWO CASES

	Cases	Per cent	Pure	Per cent
Calcium oxalate	35	67.3	26	74.2
Calcium carbonate	11	21.1	4	36.3
Sodium ureate	7	13.4	0	00.0
Calcium-magnesium phosphate	7	13.4	5	71.4
Mixed	15	28.4	0	00.0
Uric acid	5	9.6	1	20.0
Fibrin	3	5.7	0	00.0
Urostealith	1	1.9	0	00.0
Cystin	1	1.9	1	100.0

present only the gross groupings of these cases, the same being separated on their chemical basis.

RENAL CALCULI

Of the thirty-four cases of renal calculi, twelve (35.3 per cent) were the stellate phosphate of calcium and magnesium. In seven of these twelve cases this salt was in a pure state. Next in frequency was calcium oxalate, occurring eleven times (32.3 per cent) and nine times as a pure salt. Strange to say, calcium carbonate was a close third with ten cases (25.9 per cent) only three of which, however, were pure. There followed in order, uric acid and triple phosphate, each being present four times, the uric acid being pure twice and the triple phosphate once. In eleven instances (32.3 per cent) the stone was a mixed salt and the series ends with sodium ureate, three cases; fibrin, two cases, and urostealith, one case; only the last of which occurred in a pure state.

URETERAL CALCULI

In the ureteral calculi, the picture changes materially: There were fifty-two calculi analyzed and thirty-five (67.3 per cent) of these were calcium oxalate and twenty-six (74.2 per cent) of them were pure. Calcium carbonate is second with eleven (21.1 per cent) cases and four of these were pure salts. Sodium ureate and calcium-magnesium phosphate presented seven cases each, and though the former always occurred mixed with other salts, the latter in five of the seven cases, was a pure salt. Of the ureteral stones, fifteen (28.4 per cent) were mixed salts, while in decreasing numbers the following were found: Uric acid, five (9.6 per cent) cases, one of which was pure; fibrin, three cases, none pure; urostealith, one case, and mixed; cystin one case and pure.

VESICAL CALCULI—THIRTY-ONE CASES

	Cases	Per cent	Pure	Per cent
Mixed	14	45.1	0	00.0
Calcium carbonate	14	45.1	3	21.4
Calcium-magnesium phosphate	11	35.4	6	54.5
Calcium oxalate	9	29.0	3	33.3
Uric acid	5	16.1	2	66.6
Triple phosphate	4	12.9	1	25.0
Ammonium ureate	2	6.4	2	100.0
Sodium ureate	1	3.2	0	00.0

VESICAL CALCULI

In the thirty-one vesical calculi, fourteen cases (45.1 per cent) were mixed. Calcium carbonate was found fourteen times and in three instances in the pure state. Calcium-magnesium phosphate occurred eleven times (35.4 per cent) in six of the instances in the pure state. Calcium oxalate, nine times (29.0 per cent), three of which were pure. Uric acid, five (16.1 per cent) times, twice in the pure state. Triple phosphate, four times, and only once pure. Ammonium ureate occurred as a bladder stone twice, not having been found in either kidney or ureteral series even as a mixed salt,

and in these two instances it was the solitary salt present. Sodium ureate was found once, but not in the pure state.

Looking at the series as a whole, calcium oxalate heads the list with fifty-five instances in the total of 117 cases (47.0 per cent) and thirty-eight times (69.0 per cent) as a pure salt. Forty cases (34.1 per cent) presented mixed salts. Calcium carbonate, which is credited in the literature as being an extremely rare stone, was

TOTAL SERIES—117 CASES

	Cases	Per cent	Pure	Per cent
Calcium oxalate	55	47.0	38	69.0
Mixed	40	34.1	0	00.0
Calcium carbonate	35	29.9	10	28.5
Calcium-magnesium phosphate	30	25.6	18	60.0
Uric acid	14	11.9	5	35.7
Sodium ureate	11	9.4	0	00.0
Triple phosphate	8	6.7	2	25.0
Fibrin	5	4.2	0	00.0
Ammonium ureate	2	1.7	2	100.0
Urostealith	2	1.7	1	50.0
Cystin	1	0.8	1	100.0

found in thirty-five cases (29.9 per cent) and in ten of these (28.5 per cent) in the pure state. Calcium-magnesium phosphate is next with thirty instances (25.6 per cent) and eighteen times (60.0 per cent) as a pure crystallization. Uric acid was present fourteen times (11.9 per cent) and five of these were pure. Sodium ureate was present in eleven instances, none pure. Triple phosphate appeared in eight cases (6.7 per cent), twice as a pure salt. Fibrin was found in five instances, none pure. Ammonium ureate was present in two cases, both pure salts. Urostealith was present in two cases, one pure, and cystin once, and in that case a pure salt.

These findings are quite at variance with the oft-quoted statistics of the literature, and it is my belief that if this problem of calculus

formation be divided into its separate chemical chapters and studied intensively as separate problems, greater progress will be made in its elucidation, representing as it does today, a severe criticism of the progress of urology.

SUMMARY

	Series Total	Kidney	Ureter	Bladder
Number of cases	117	34	52	31
Calcium oxalate	55 cases 47.0% 38 pure	11 cases 32.3% 9 pure	35 cases 67.3% 26 pure	9 cases 29.0% 3 pure
Calcium carbonate	35 cases 29.9% 10 pure	10 cases 25.9% 3 pure	11 cases 21.1% 4 pure	14 cases 45.1% 3 pure
Sodium ureate	11 cases 9.4% 0 pure	3 cases 8.8% 0 pure	7 cases 13.4% 0 pure	1 case 3.2% 0 pure
Uric acid	14 cases 11.9% 5 pure	4 cases 11.7% 2 pure	5 cases 9.6% 1 pure	5 cases 16.1% 2 pure
Calcium-magnesium phosphate	30 cases 25.6% 18 pure	12 cases 35.3% 7 pure	7 cases 13.4% 5 pure	11 cases 35.4% 6 pure
Triple phosphate	8 cases 6.7% 2 pure	4 cases 11.7% 1 pure		4 cases 12.9% 1 pure
Double or triple mixed deposits	40 cases 34.1%	11 cases 32.3%	15 cases 28.4%	14 cases 45.1%
Fibrin	5 cases 4.2% 0 pure	2 cases 5.8% 0 pure	3 cases 5.7% 0 pure	
Urostealith	2 cases 1.7% 1 pure	1 case 1 pure	1 case 1.9% 0 pure	
Ammonium ureate	2 cases 1.7% 2 pure			2 cases 6.4% 2 pure
Cystin	1 case 0.8% 1 pure		1 case 1.9% 1 pure	

QUALITATIVE ANALYSIS OF URINARY CALCULI

(Hammarsten-Heller-Beck)

Calculus has been cleaned, dried and pulverized:
Heat a portion of the powder on a platinum foil:

A. If powder does not burn it is inorganic material:
   a. Add HCl acid:
      1. If effervescence—*Calcium Carbonate.*
      2. No effervescence—proceed to *b.*
   b. Heat a portion of the original powder gently in an evaporating dish and add HCl acid:
      1. If effervescence—*Calcium Oxalate.*
      2. No effervescence—proceed to *c.*
   c. Treat a portion of the original powder with KOH:
      1. Ammonia odor evolved; powder is soluble in acetic acid and a crystalline precipitate forms on addition of ammonia water—*Triple Phosphates.*
      2. If no ammonia odor evolves, or only traces, and the powder dissolves in acetic acid or HCl acid, add NH_4OH—amorphous precipitate—*Calcium and Magnesium Phosphates.* May check crystalline triple phosphates and amorphous Ca. and Mg. phosphates by microscopic examination.

B. If powder burns it is organic material:
   a. If burns with flame:
      1. Flame yellow and continuous. Odor of burning feathers. Insoluble, in alcohol or ether. Soluble in warm KOH. Precipitated by acetic acid with evolution of H_2S gas—*Fibrin.*
      2. Flame pale yellow and continuous. Odor of resin. Soluble in alcohol or ether. Absorbs fat stains—*Urostealith.*
      3. Flame pale blue and brief. Peculiar sharp odor. Soluble in NH_4OH, with separation of six-sided plates on evaporation—*Cystin*
   b. Without flame: To powder—
      1. Apply the *Murexide Test:* Moisten the original powder with a few drops of strong HNO_3 acid. Evaporate this to dryness in an evaporating dish at a temperature not exceeding 110 degrees Fahrenheit. A yellowish or brownish mass remains. To this add a drop of NH_4OH. A purple color appears. Add a drop of NaOH solution. If a violet color appears, the test is positive. The powder contains a metallic urate, which is probably *Sodium Ureate.*

2. If ammonia odor evolves on the addition of NaOH—*Ammonium Ureate.*
3. If no ammonia or little ammonia evolves on the addition of NaOH—*Uric Acid.*
4. If the dry, yellow mass becomes orange with the addition of NaOH and then red on gentle warming—*Xanthin.*

Re-agents used:

1. HCl (concentrated).
2. NaOH (10%).
3. Acetic Acid.
4. NH_4OH (concentrated).
5. Alcohol.
6. Ether.
7. KOH (10%).
8. HNO_3.

If the calculus is sufficiently large, wrap it in a piece of paper and saw it into halves. Peel off each layer separately, and reduce each to a fine powder. Examine each layer separately and try to determine the component of each layer and the nucleus.

THE MANAGEMENT OF BILATERAL URINARY CALCULI

ALEXANDER R. STEVENS, M.D.

From the Urological Service of Bellevue Hospital, New York City

The problems associated with bilateral urinary calculi have given rise to a fairly extensive literature, wherein are expressed various opinions, sometimes contrary, relating to the management of these cases. Obviously, all the questions which arise in dealing with the simpler unilateral disease must be considered first. We must know the location of stones, the function of both kidneys, the presence or absence of infection and of symptoms, the status of the patient's other vital organs, and, especially during these days, it is only just to take account of the patient's social and financial responsibilities. Our purpose now, however, is to consider only the added judgments required when calculous disease of the upper urinary tract is bilateral.

Our first question after a decision is made to operate is where to begin and how much to do; for it is generally agreed that in most cases simultaneous bilateral operation is hazardous, and hence one of our most important decisions concerns the choice of the side for the first attack. In recent times it is the advice of most writers that one should operate on the "better side" first. Exceptions are made here and there. But how may one determine the better, the functionally more capable kidney? Does one guess at it, or does his judgment depend on tests of renal function? Our commonly employed tests for comparing two kidneys give us some notion of their ability at the moment of examination only, and are notoriusly unreliable as indicators of what a kidney may do under altered conditions. One wants this information by all means, but in the presence of calculi the surgeon is skeptical in his interpretation of the tests, and leans heavily on the history and on the information obtained from x-ray examinations, particularly the location of stones, to determine his course of action. In practice, lowered renal function tests of one kidney have often been an argument

with me in favor of operating on that side, when a stone is so placed that it may obstruct.

In bilateral nephrolithiasis, or with ureteral stones on one side and multiple renal stones on the other, it has been suggested that the first operation should usually be on the side with recent acute symptoms. As such pain is most likely due to partial obstruction,

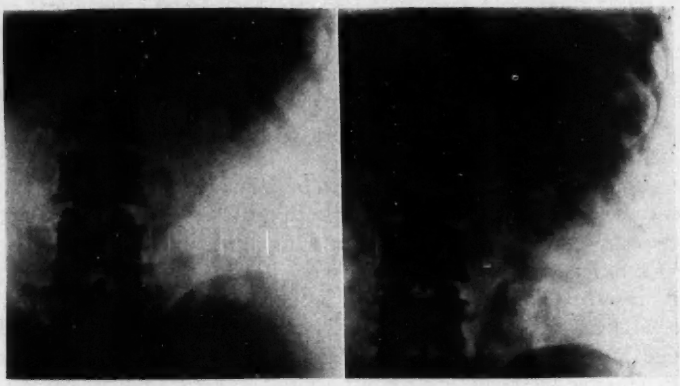

Fig. 1 *(left)*. Case 1. Woman, aged forty; much pain in left flank past two weeks; similar attacks for four years; no urinary disturbance. Marked tenderness of left kidney. Fair function of left kidney, some infection; right ureteral orifice not found, no indigo-carmine seen in twenty minutes; intravenous urogram showed good output from left kidney and none from right. Large calculi in lower right ureter and stag-horn calculus in left kidney. Pain and tenderness in left kidney became less in hospital. Right ureterotomy, with removal of two calculi. Intravenous urograms two weeks after operation showed slight excretion from right kidney (recent case, still in hospital).

Fig. 2 *(right)*. Case 1. Intravenous pyelogram taken before operation. Operated first on right ureteral calculus.

that working rule will often be helpful; but I should rather have a look at the roentgenograms before deciding. In a recent case, I deliberately operated on the side opposite to that complained of (Figs. 1 and 2).

After all, as one reads the reports of the more experienced workers, he finds them grouping cases, and suggesting the management of each group. Others will cite a long series of individual case reports, detailing the argument for the course adopted in the particular case. So that, after all, the management of bilateral calculi

sifts down to a thoughtful study of each problem after the accumulation of much data.

One must consider the possible symptoms and the damage to the kidneys which stones may cause, and balance that against the probable good or harm which may be expected to follow different operations. If a stone is causing neither pain nor hematuria, if it is so placed that it probably will not obstruct the urinary outflow and is not associated with infection, there is little excuse for disturbing it unless, perhaps, it grows rapidly and the operator feels an earlier and easier operation is for the patient's ultimate good. To my mind, obstruction is the most important of these factors for us to consider, in that it may rapidly cause serious damage to the renal cortex. Moreover, infection associated with calculus is particularly vicious when obstruction is present; also, we would note that severe pains usually occur only when a stone is obstructing.

On the other side of the picture, gentle handling of a kidney at operation with incision in the ureter or pelvis depresses renal function little, if at all, temporarily or permanently. Whereas, a large cortical incision or multplie small ones, often sharply reduces kidney function, both immediately and remotely.

These considerations appear to me to be more rational and more valuable as guides in dealing with the problems under discussion than the commonly repeated rules. The most widely preached formula, to operate first on the side with the better kidney, is vague and misleading. We should aim at doing the greatest good, particularly to renal function, with the least harm. An obstructing calculus usually demands first attention; and as its removal is generally accomplished without a cortical incision, little harm is done.

When there is no apparent obstructing stone, one does well to attack the kidney with fewer stones first, if both sides require operation. That is usually the better kidney as a matter of fact. But regardless of this factor the point I would stress again is that the reason for operating first on this kidney rests on the fact that one will likely get rid of these stones through a pyelotomy incision or at least with the minimum damage to the parenchyma, avoid the hazards of possible hemorrhage and acute infection associated with nephrotomy, and depress the total renal function as little as may be. Thus we will be placed in a comfortable position to deal with the other kidney (with the greater number of stones), to re-

move it if necessary. When there are small stones easily reached by ureterotomy or pyelotomy incisions, and the patient's general condition and renal function tests are good, I see no objection to simultaneous bilateral operations if the first operation is quickly done.

Fig. 3. Case 2. Man, aged thirty-one; no pain or urinary symptoms; general symptoms, including high blood pressure, headaches and flushing of skin. Function tests of right kidney but little better than left. Total phthalein output 25 and 15 per cent for two hours; N.P.N. and creatinin of blood normal. Multiple calculi of both kidneys with large stones in both pelves. Left pyelotomy and multiple nephrotomy incisions; over 200 stones removed. Oliguria and death on third day after operation (see text).

A review of thirty-three cases of bilateral calculi of the upper urinary tract which came to operation (all but three of which are from the urological service at Bellevue Hospital), has been made, and both successes and failures are offered as a basis for our present views. These patients include one operated upon in 1916, one in 1919, but the remainder were seen first between 1921 and 1933.

I have not included cases of bilateral stones which passed through

our hands without receiving surgical treatment for this particular condition. There were bilateral calculi without symptoms found

Fig. 4. Case 3. Man, aged thirty-six; many stones passed, following ureteral colic on both sides during past year; for four months in another hospital with acute multiple arthritis, septic temperature and frequent right renal colic with passage of stones; very ill on admission. Thick pus from right ureter and practically no function of right kidney; little pus from left kidney and fair function. Total phthalein output 25 and 15 per cent. Large groups of calculi in right kidney, and many small stones in left. Right nephrectomy performed, with prompt and marked improvement in general condition and acute joints. During next six months passed spontaneously all but two stones from left kidney. Total phthalein output for two hours, eight months after operation, was 58 per cent.

incidentally in patients ill of medical ailments, for whom no treatment of the urinary tract was advised, and other patients admitted

to our own service who refused complete examinations or treatment. I do not include two patients who came to operation for stone in a single kidney after the other kidney had ben removed elsewhere for calcareous pyonephrosis.

As illustrations of advanced cases, beyond the help of surgery, I might cite two instances. One man, with bilateral stones, was uremic on admission, with N.P.N. 145 mg. and creatinin 3.6 and ribbons of pus coming from both ureteral orifices. The condition became gradually worse and the man died. Another patient had had stones removed from his right kidney elsewhere three years before, and had been advised to return for a similar operation on the other side. But he sought no further aid until pain and hematuria became marked. On admission to our hospital the N.P.N. was 128, and creatinin 10. The old stag-horn calculus was still present in the left kidney and multiple stones had recurred on the right side. The patient died in uremia on the tenth day.

Of the thirty-three patients *who came to us with bilateral calculus and were operated upon,* three had simultaneous bilateral operations with no deaths. One was for anuria, due to bilateral ureteral stones. There were five deaths after the first operation among the other thirty. Nine of the group came to operation on the second side, and of these, one died. Many of those individuals who had operation on but one kidney should have submitted to similar surgical attention on the other side, but they failed to return for this treatment, however, probably because free from pain.

Our five deaths following the first operation included one which occurred in a very ill man, three days subsequent to simple incision for peri-nephritic abscess with no attempt to remove the calculus. His N.P.N. on the day of the operation was over 200.

The second death followed drainage by pyelotomy performed upon the right kidney, with removal of one obstructing stone, for recurring anuria. This man, fifty-two years old, entered the hospital with anuria following a drunken debauch, and was relieved on four or five occasions by catheters placed in both ureters. Each time the catheters were removed, the urine would cease, the patient would become uremic, the nitrogenous blood elements would rise, and then the catheters would have to be replaced. Once after withdrawal the N.P.N. reached 230. But the cystoscopic treatment could not be continued indefinitely and we chose what was

a relatively favorable interval for the operation, when the N.P.N. was 56 and creatinin 3.2. Autopsy showed calcareous incrustations on the wall of the right ureter just below the pelvis, and a calcareous deposit obstructing the uretero-pelvic junction on the left side; both kidneys were badly infected.

The third death followed operation for removal of over 200

Fig. 5 *(left)*. Case 4. Simple x-ray film. Man, aged forty-four, dull pain in right flank past two or three weeks, with no other history of pain nor of any urinary frequency. Function of two kidneys about equal, slight bilateral infection. Two large calculi in calices of right kidney with faint diffuse shadows in lower pole; one large calculus in lower major calix of left kidney, with diffuse shadow in lower pole. No stone in either renal pelvis or ureter. Left nephrotomy for stone and resection of lower quarter of kidney for latent tuberculosis. Patient did not return for further observation.

Fig. 6 *(right)*. Case 4. Bilateral calculi with double pyelograms.

calculi by pyelotomy and multiple nephrotomy from one of two kidneys, both of which contained a large (and about equal) number of stones (Fig. 3). Before operation the N.P.N. was normal, and the total phthalein output 20 per cent and 20 per cent for the first two hours. The kidneys were of about equal functional value. In spite of our best efforts the urine output subsequently was very scanty, the N.P.N. rose steadily, and the patient died on the third postoperative day.

The fourth death occurred five days after primary removal of a pus kidney, and apparently was due to extreme abdominal distention—quite likely an evidence of renal insufficiency.

The fifth death was due to shock and followed removal of the poorer kidney through the scar of a former operation for high ureteral calculus.

Fig. 7. Case 5. Man, aged forty-eight; had had left pyelotomy for calculus twelve years earlier; calculi found in both kidneys four years ago, also pyuria and hematuria. Past six weeks much pain in both kidney areas, worse on right. Right kidney urine thick with pus, function almost zero; left kidney moderately infected, function good. Large dendritic calculus in right kidney; multiple calculi in left kidney. Left pyelotomy and four nephrotomy incisions. Two small pieces of stone remained. N.P.N. and creatinin rose from 45.0 and 2.2 before operation to 100.0 and 4.3 on tenth day after operation, and dropped to 37.0 and 1.5 on twenty-fourth day. Five months later, right nephrectomy of pyonephrotic kidney. Phthalein output for two hours, before first operation, 45 and 20 per cent; best after first operation, 20 and 15 per cent; four years after both operations, 30 and 5 per cent and urine free from pus; very slight increase in size of stones in left kidney. General health excellent.

The first two deaths, I believe, were inevitable. Perhaps we should have allowed the third patient to live without operation as he had no pain symptoms, but he was only thirty-one years old and was beginning to complain of headaches and other symptoms which we felt were due to decreasing renal function in spite

of fairly satisfactory tests. The grave risk was discussed with him and his family, and operation was decided upon, hoping to prolong life and make it more comfortable. Preliminary nephrostomy might have offered a better prospect or perhaps I should have merely removed the large pelvic stone by pyelotomy. On reviewing the fourth case, I think the attack was on the wrong side. The right kidney (which was removed) contained a dendritic calculus, discharged pus from the ureter, gave no evidence of any function and was the seat of pain. The left kidney contained a large stone in the pelvis, was free from infection, and gave a good urea percentage and indigo-carmine in seven minutes. Possibly primary removal of this stone through the pelvis would have been better practice, but we removed the worthless kidney—the one causing pain. The fifth case was a parallel one, though the functional difference between the kidneys was not so pronounced, and the better kidney contained a staghorn calculus. The poorer kidney, the one giving pain, was removed. But as the patient died of shock within twelve hours after a difficult subcapsular nephrectomy through an old operative scar, this case is not enlightening to our present problem.

I should like at this point to refer to the one successful primary nephrectomy. This patient had suffered for months with multiple, acute, infective arthritis, and was running a high septic fever daily. Roentgenograms showed numerous calculi in both kidneys (Fig. 4). Removal of the right, the worse kidney (as regards function and infection) was followed by immediate relief of the general symptoms and the arthritis. This course was urgently indicated because of the serious general septic condition. During the subsequent months of convalescence the patient passed nearly all the stones from the other kidney! There was no very large stone in this better kidney, and none in the pelvis, however, as was the case in the two patients who died following nephrectomy.

There was one case of nephrectomy required for secondary hemorrhage following nephrotomy for stone. In another patient I resected the lower third of the left kidney for an old, inactive tuberculosis and removed the stones present (Figs. 5 and 6). A similar condition seemed to be present on the other side—well defined stones in the upper part of the kidney and irregular calcareous deposits (probably old tuberculosis) in the lower portion.

But the man did not return for further observation and possible operation on the other side.

Nine of the thirty patients who had had operation on one stone-bearing kidney or ureter came to operation on the other side. These second operations were performed at intervals varying from seventeen days to a year after the first operation. Nephrectomy was

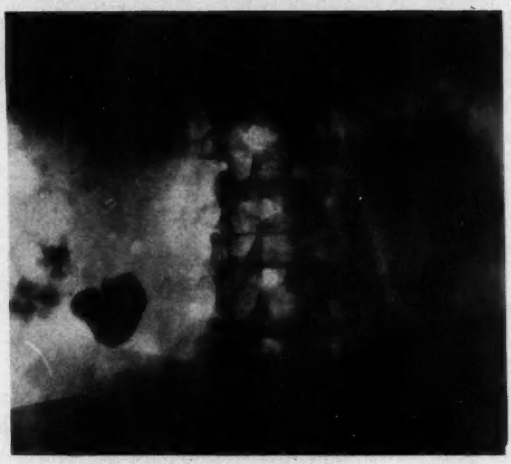

Fig. 8. Case 6. Woman aged sixty-eight; many attacks pain in right flank past five years; calculi passed three months ago following pains on both sides. Function of left kidney nearly twice that of right, no infection of either; large stone in right pelvis and multiple jack-stones and small bits in right major calices; few small stones scattered in left kidney. Right pyelotomy and one nephrotomy incision. Few very small pieces remained, but passed spontaneously from kidney. Operation not advised on left side.

required but once; recovery was rapid (Fig. 7). There was one death in this group of nine; operation on the second kidney had been postponed until a year after the first one, and was done only after serious pain was felt in the corresponding kidney. Death was due to renal insufficiency and occurred eighteen days after removal of a stag-horn calculus through multiple nephrotomy wounds.

One of our earliest cases and a particularly interesting one from the diagnostic point of view, was a man thirty-two years old whose

roentgenograms showed multiple calculi in the right kidney and one large one apparently in the pelvis of the left. On ureteral catheterization much more urine was obtained from the right side than from the left, and a larger amount of phthalein was recovered from the right side. However, the percentage of urea and the

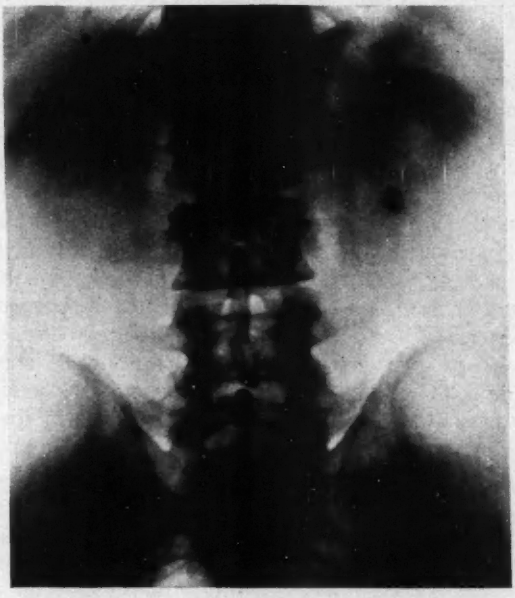

Fig. 9. Case 7. Man, aged sixty; pain in left kidney area, three months. Right kidney function excellent; left function, almost zero. Calculus in calix of right kidney; calculus blocking left uretero-pelvic junction. Left pyelotomy. Function of two kidneys about equal, seventeen days after operation. Operation not advised on right side.

depth of color of the dye were much better on the left side. These findings were confirmed by a second cystoscopy. The conclusion was that the left kidney was of better quality than the right, but must be very small. At operation an infantile kidney was found on the left side and the stone removed from its pelvis. Feeling that I had accomplished little, I turned the patient over and imme-

diately exposed the right side and removed a large group of stones from that kidney; but x-ray films taken later proved we had left several small ones. The patient went home comfortable and apparently in good condition, but returned to the hospital six months later and died of uremia twelve days after nephrostomy. This case is cited as a warning to pay strict attention to the quantity of output from the kidney as well as the quality.

It has been interesting to tabulate the relative functions of the two kidneys at the time of examination, and note on which side the first operation was performed. Obviously we exclude the three cases with simultaneous bilateral operations, and others where no choice between sides had to be made. There were eight primary ureterotomies for stone on the side of poorer function as indicated by the tests (routinely we compare the urea percentage and the output of phenolsulphone-phthalein or indigo-carmine), and none on a side presenting better function. Pyelotomies (with additional nephrotomy at times) were done six times on the poorer side, four on the better side, and six times when the two kidneys seemed to function equally well. Primary nephrectomy of a poorer kidney was done three times. Our experience warns against such a course when a stone, possibly obstructing, exists in the ureter or pelvis of the better kidney.

Our aim has been to improve the total renal function as much as possible by the first operation, with the least risk. By obstructing the urinary outflow a calculus does the greatest harm to the kidney and in the shortest time, and relief of the obstruction is our first object. Hence, ureteral stones, when present on the side of lessened function, were the objects of prompt attention. Pelvic stones also may be so placed as to obstruct markedly; hence the more frequent, early removal of these stones from the side of lowered function. Renal stones not obstructing may grow very large and exist a long time without an appreciable decrease of renal function, but their removal, especially when extensive nephrotomy incision is required, may cause damage with serious immediate and permanent decline of function of the kidney. Some of these kidneys should not be operated upon as the operation may do more damage than the stones, as has been frequently pointed out. The size, number and location of calculi as revealed by x-ray films, the total renal function, and the presence or absence of infec-

tion are more important factors than symptoms and relative function of the two kidneys in helping us to decide on which side to operate first.

It has been interesting to note that when pain in either kidney region was a complaint at the time of admission to the hospital, our reasoning as above outlined has in most cases led us to operate on the painful side.

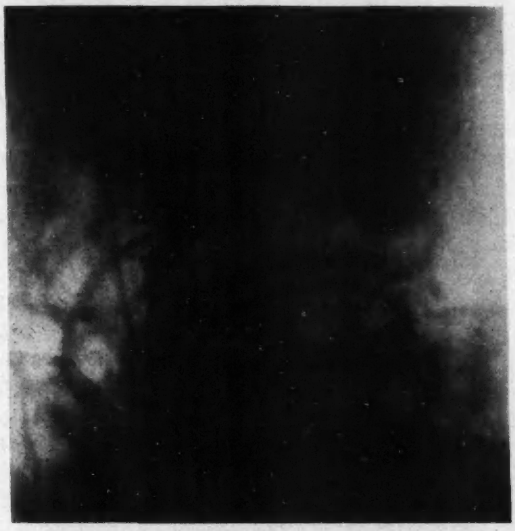

Fig. 10. Case 8. Man, aged forty-eight; occasional hematuria for six months but no pain. Function of both kidneys good and equal, neither infected. Medium, non-obstructing stone in right upper major calix; large non-obstructing stone in left pelvis and major calix. Left pyelonephrotomy. Patient did not return for operation on otherside.

One may well wonder what happens to these victims of bilateral calculus disease, after finishing with the surgeon. All patients were relieved of pain and hematuria. The function of the kidneys involved, as evidenced by the usual tests, showed great improvement when definite obstruction was relieved. One patient with anuria, with N.P.N. 107 and creatinin 4.5 was subjected to bilateral ureter-

otomy for stones, with almost immediate return of the flow of urine and quick general recovery. Seen seven years later, he appeared hale and hearty.

In some instances, the removal of non-obstructing stones from kidneys was not followed by better laboratory tests for renal functions; and, in fact, sometimes these tests were worse after nephrotomy incisions. While it is amazing how high these tests may place the capabilities of a kidney full of stones and even harboring an infection, it is to an equal degree disturbing to note the early sharp decline of function which may follow multiple nephrotomy and the manipulation incident to the removal of the calculi. Later tests may equal but usually show no improvement over those made before operation. We know that calculi, not obstructing, and without collateral infection, may be present a long time in a kidney without causing destruction. Hence, under such circumstances, many such cases are well let alone. Unless stones are growing rapidly, the non-obstructing ones cause destruction of the kidney very slowly.

We have had relatively few opportunities for late observation on our operated cases, but such observations have noted definite decrease in the evidences of infection in some of the kidneys from which stones were removed, in some instances within a few weeks. A most satisfactory observation was of a man who passed urine free from pus four years after multiple nephrotomy for stones in one infected kidney and nephrectomy for caculous pyonephrosis on the other side (Fig. 7).

The ordinary handling of a kidney at operation with pyelotomy or ureterotomy does not interfere much, even temporarily, with the blood N.P.N. figures taken at intervals after operation. But when nephrotomy incisions, especially if multiple, are made in the better kidney, my experience points to a definite rise (once to 100 mg.) in a week or ten days. I have but few records to support that belief, but this possibility is worth remembering in postoperative treatment.

Our patients operated upon for calculus are routinely examined by x-ray before they leave the hospital. Occasionally stones of moderate size have been found. When we have encountered groups of small pieces with sand, some of this is almost invariably left in spite of copious irrigation. X-ray employed at the operating

table has helped locate larger pieces, but is of little assistance with the finer particles. One may scoop and irrigate conscientiously, but it is practically impossible to get rid of all bits. However, it

Fig. 11. Case 9. Man, aged forty; entered medical wards with bronchitis; has had three attacks of renal colic, last one five years ago, but no urinary symptoms now. Total phthalein output, 10 and 10 per cent for two hours; right kidney showed slightly better function than left. Multiple calculi in right kidney and long one in upper ureter; single stone in upper pole of left kidney and long one in upper ureter. Left pyelotomy and nephrotomy; nine days later, function of left kidney more than twice that of right, and general phthalein output 20 and 5 per cent. Seventeen days later, right pyelotomy and multiple nephrotomy. In six months, general phthalein output 25 and 20 per cent. Eighteen months after second operation small stone left in right kidney blocking right ureter. Right nephrectomy was done for pyonephrosis and perinephritic and peri-ureteral abscesses were encountered. Nine days later, phthalein output was 30 and 15 per cent for two hours.

is not uncommon for patients to pass some of these later (Fig. 8). Fortunately the presence of a few small pieces does not necessarily give a bad prognosis, as observation of urinary calculi by x-ray films over long periods of time has shown a great variability in the rapidity of growth; some stones will show little or no increase in size in years.

In conclusion, let me urge a careful general survey and an especially painstaking and complete urologic examination of patients carrying bilateral urinary calculi.

I would emphasize the fact that our renal function tests indicate the ability of the kidneys under the existing conditions only, and frequently offer an erroneous idea of their real worth, particularly in the presence of calculi. One must consider each case on its own merits, and decide whether to do anything and what. Immediate improvement of function and infection and the ultimate preservation of the maximum function of the kidneys by the least harmful means should be our goal.

When the stones are easily reached through pyelotomy or ureterotomy incisions, simultaneous bilateral operation is justifiable on patients in good condition and with kidneys functioning well, if the operations are quickly done. But in the majority of instances it is wiser to operate on but one side at a time. The usual advice to operate first on the better kidney is misleading. Although we often do operate first on the side of recent acute pain, the site of pain does not offer a safe guide. It is better that an improvement of renal function be our chief consideration. Relief of obstruction in the urinary tract is our chief mode of helping renal function, and that usually means the primary removal of ureteral calculi or obstructing pelvic calculi, when present. Such operations imply the least harm, in that incision of the parenchyma of the kidney will probably not be required. If an acutely infected kidney is present, it will probaly be the one so obstructed and hence will be benefited by the procedure.

In bilateral renal calculi with no obstructing elements, one should usually operate first on the side which contains the smaller stone or smaller group of stones (which is usually the side with better function), especially if they be so situated that they may be reached without incising the cortex; nephrectomy may be needed on the other side.

The greater the number or length of nephrotomy incisions, the greater the damage (both transient and remote) done the kidney by operation. The fewer the sutures used in the cortex of the kidney, the less will be the amount of substance strangulated, the better the ultimate function. Emergency secondary nephrectomies for acute infection or hemorrhages following such operations will be fewer. Small incisions, especially through thinned parenchyma, often need no suture to control bleeding.

Many kidneys full of stones and those occupied by stag-horn calculi may better be left alone in the absence of symptoms.

The scope of this paper does not include a consideration of the preoperative treatment, always helpful and frequently essential, in the proper management of bilateral renal calculi. Nor can we touch on the necessary directions and attention which should follow operation, using all our knowledge and means to prevent recurrences of stone formation.

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END-RESULTS OF OPERATIONS FOR LITHIASIS

WILLIAM C. QUINBY, M.D.

Boston, Massachusetts

In the five years preceding 1931, that is during the years 1926, 1927, 1928, 1929, and 1930, there were 240 patients admitted to the Peter Bent Brigham Hospital suffering from renal or ureteral calculus. This time period marks the beginning of our endeavor to adopt a consistent policy in regard to urinary stone which was as follows: (1) To conserve renal tissue whenever possible and thus employ nephrectomy only when the renal damage was great; (2) to consider the operation which removes a stone only the first event in the medical care of the patient and to insist that whenever possible each patient return at suitable intervals for antiseptic treatment of the bladder and kidneys; (3) in instances needing operation, to persist until the x-ray film taken at the operating table, showed that all stones had been in fact removed.

Of this total number of 240 patients, seventy-six general hospital patients and forty-five private patients have made themselves available for the present analysis. An x-ray was taken of all the general patients when returning, a physical examination was made, and the urine analyzed and cultured. Letters from the patients or their doctors were at times taken instead of a personal interview on the part of some of the private patients. One hundred and twenty-one patients are considered.

There was an immediate operative mortality in one case. Three other patients failed to be relieved of their malady and later died of it, giving a total mortality of 3.3 per cent.

In fifty-four patients the calculus was found in the ureter only. These were treated by ureterotomy in thirty-three instances, while in twenty-one either intravesical cystoscopic manipulation or expectant treatment was instituted. Though in four of these cases there was recurrence of stone in the ureter at a later period, at the time first seen or shortly thereafter all were relieved of their stone.

In sixty-four cases the stone or stones were situated in the kidney; in three the stones were in both ureter and kidney. There

were six cases of bilateral stone and two patients were instances of stone in a single kidney.

On the follow-up record of the renal stone group we found that stones had recurred in twenty instances (in five of the bilateral cases all the stones had not been removed at operation). Therefore, of 121 cases, twenty-four or 19.8 per cent still showed stone.

Further analysis has shown that failure to relieve these patients permanently has in almost all instances been due to a persistence of the original infection. It is therefore clear that after a certain degree, or chronicity, of infection has taken place in a kidney we are well nigh powerless to conquer it, even though persistent effort be made after the stone has been removed.

There were twenty-four nephrectomies as against forty-five cases in which the calculus was removed by pyelotomy or pyelonephrotomy. Though the majority of the nephrectomy patients were cured, in three the subsequent formation of multiple stones in the remaining kidney led to further operations and eventual death in two instances.

From this study it appears that:

1. Cases of ureteral stone are apt to be associated with less infection and less damage to the kidney than those instances in which the calculus has not entered the ureter. This is doubtless largely due to the fact that urgent symptoms are caused by these relatively small stones at a much earlier date.

2. Cases of renal calculus should be subjected to operative removal of the stone at an early date. It is a mistake to delay operation because the stone is causing no symptoms at the moment.

3. The problem of urinary infection plays a large rôle in the incidence of stone formation, and the end-result of the treatment of stone depends, to a great extent, on the degree of such infection and our ability or inability to conquer it.

DISCUSSION

PRESIDENT FOWLER: This group of papers is now open for discussion, but before opening them for general discussion, we have with us this morning Dr. Sullivan, Director of Chemo-Medical Research at Georgetown University, and I am going to call on him to open the discussion on Dr. Kretschmer's paper.

DR. M. X. SULLIVAN (Georgetown University): I was fortunate enough this morning to note on your program the papers on cystin and cystinuria. For a number of years I have been interested in the biochemistry of sulphur and have developed tests of remarkable specificity for the system—cystin, cystein, and glutathione. Recently, I have become interested in cystinuria, so I came to listen and to seek your aid.

The Sullivan test spoken of by Dr. Kretschmer is a test for cystein ($CH_2SHCHNH_2COOH$), but can be used for cystin (after reduction) or for cystin complexes such as glutathione after hydrolysis and reduction.

The test is so specific it requires that the three chemical groups in cystein (SH), (NH_2), and COOH be free. It is not given by iso-cystein ($CH_2NH_2CHSHCOOH$).

Application has been made of the tests to purified foodstuffs, enzymes, hormones, normal blood, et cetera, but as yet no detailed application has been made to urines in health and disease.

In 1929, by request, I worked with normal urines and found it a difficult field. I decided, however, that there were cystin complexes in normal urine, but very little free cystin, and gave a paper on the subject at the International Congress for Physiology in Boston, 1929. There I became acquainted with Dr. Brand who came out with a paper on cystinuria, a case in which the freshly voided urine did not give my test, but did on standing.

Because of a change in my work from the United States Public Health Service to Georgetown University, I had to defer further work on cystin in the urine in health and disease. At Georgetown, my lines of work have been the attempt to devise tests of diagnostic value in the urine in cancer and in this study I was brought in con-

tact with arthritis which seems to offer an interesting and important sulphur question.

Recently, with Dr. W. C. Hess, I have covered various hormones of the glands of internal secretion and various enzymes. Most of the hormones contain cystin. We verified the findings of du Vigneaud that insulin contains about 8.5 per cent cystin. We found that McArthur's posterior pituitary hormone contains over 12 per cent cystin. Thyroglobulin is rich in cystin. All the enzymes that came to our hands except invertase contained cystin.

I wish to give you the idea that the sulphur system is important because it is one of the prominent protective systems in our body and plays a rôle in the action of enzymes and hormones.

A number of years ago, in a comparative study of various cystin tests, we had occasion to study the cystin content of finger nails. The normal finger nails of white Americans contained on the average 12.5 per cent cystin. The lowest normal gave 10.8 per cent. Later we studied the finger nails of arthritic patients and found that in this abnormality the finger nails tend to run low in cystin. Of 100 arthritics patients, eight were in normal levels of 11 to 13 per cent, but the average of the 100 was 9.8 per cent. Some ran as low as 6 per cent. My idea was that the low cystin content of the finger nails implied an intoxication of some kind and that the sulphur system was being used to defend as far as it could.

The principal reason for my coming here is that a short time ago we analyzed the finger nails in a case of cystinuria. The cystin content of these nails was 8.2 per cent, whereas our normal patients gave an average of 12.5 per cent. We would like to have analyses of the finger-nail clippings of cystinuric patients, and would be pleased to make such analyses for you if you would send us the clippings, say, of one or both hands, or hands and toes preferably separate. It might give us a new insight into the sulphur metabolism in cystinuria. At any rate, we crave the aid of you who are interested in this abnormality, cystinuria.

Dr. E. G. Crabtree (Boston, Mass.): Before we get off the question of cystin, I want to present a case which showed difficulties arising in the course of convalescence, due to two errors, one of which was made by the pathologist in failing to analyze the whole stone, and the other by myself in failing to recognize the significance of crystals in the urine.

The patient was a young man of twenty-five who had led an active life. He was a short and heavy man. He had no past history of disease, except asthma up to the age of fourteen, until two years ago when he presented one acute attack of left renal colic. In the two years intervening he had constant dull pain on this side. His right kidney had never given symptoms. There had been no instance of the passage of calculi or of crystals that had met his observation. The calculus was shown by the x-ray very clearly. His routine examination was negative in all respects except that he had a few pus cells in the urine, evidently a low-grade urinary tract infection. His chemistry was normal although cystin chemistry was not done.

At cystoscopy, the left kidney was shown to have no function. There was a 30 per cent function on the right. There was a completely negative right urine.

The operation done was nephrectomy. The first eight days of convalescence were quite normal except that the patient had gas, as a short, thick man would be apt to have, which was a little troublesome, but soon righted itself.

On the eighth day the patient showed suppression of urine. Believing that a small stone had been overlooked in x-ray, cystoscopic examination was made, and at cystoscopy the kidney pelvis was found to be distended with concentrated urine, such as a good functioning kidney would give. No obstruction was observed in the passing of the catheter up that ureter. Pyelography was repeated and was negative. After the cystoscopy, the patient passed water normally except that there was some sand in his urine which I interpreted as probably due to the breaking up of a small, soft calculus. This proved to be one of the first errors made.

In the course of the next two days, the patient took fluid and voided normally, but again became obstructed. Cystoscopy was again used and the patient was again relieved, but the same afternoon he became obstructed again, and at that time very little fluid was obtained from the pelvis. This led to immediate pyelotomy. At operation, the kidney was normal appearing with the pelvis much distended. When opened, there was very little urine, but a great amount of fine, sharp sand. This was analyzed and eventually proved to be cystin crystals. Pyelotomy drainage was established.

The second error was in the analysis of the calculus. The first analysis of the stone was incomplete and the report was calcium and magnesium phosphate. This, unfortunately, was done from fragments of the stone and not from the whole stone. After the finding of cystinuria in the opposite kidney, the whole stone was examined again, and was found to contain pure cystin.

The patient's urine was alkalinized. The diet was changed to vegetable diet with the proteins supplied in the forms of egg and milk. The patient quickly cleared up, made an uneventful convalescence, and is now in the hands of some chemically-minded men who have found him clear of cystin calcification and requiring less and less alkalinization to keep him so.

CASE REPORT

Newton Hospital.
October and November, 1932.

J. McG., male, aged twenty-five years, single, clerk, had asthma up to fourteen years of age and has had none since. Tonsillectomy in childhood.

Two years ago he had one attack of severe, colicky pain in the left renal region and radiating downward but not to the genitalia. This pain was of about five hours' duration. It was followed by three days' local tenderness and soreness on motion. There has been a dull ache in the same region, of frequent occurrence in the two years since the initial attack, but never a recurrence of colicky pain. Three days before admission he noted a throbbing sensation in the left flank which has been constant since onset.

Neither before nor since the initial attack have there been colicky pains in either kidney region, suggesting the passage of gravel or crystals. There have been no symptoms referable to the right kidney at any time in the history.

The character of the urine was not noted except that it had been cloudy for a long time.

Physical examination was negative except for voluntary spasm and tenderness in the region of the right flank. The patient is a short, heavy man, of good musculature and evidently of outdoor habits.

Laboratory data on admission.—Bladder urine—Cloudy, sp. gr. 1018, acid, albumin small trace, no sugar, sediment loaded with pus, rare red cells. White blood count, 13,400; red blood count, 4,310,000; smear—neutrophiles, 79 per cent; lymphocytes, 21 per cent; no anemia shown in red cells. Hemoglobin—90 per cent. Non Protein Nitrogen—35 mgs. Blood Sugar—91 mg. Phthalein test—first hour, 42 per cent; second hour, 12 per cent; total, 54 per cent. Wassermann test—negative.

Plain x-ray showed a large lobulated and laminated calculus in the region of the left renal pelvis. The outline of that kidney was not visible. The right kidney outline was distinctly larger than normal and there was no evidence of stone. The ureters and bladder regions were not remarkable.

Fig. 1. The pyelogram on which the diagnosis was made. The right pelvis and ureter are normal. The left pelvis is obstructed by a calculus which shows clearly by x-ray.

First cystoscopic examination was done the second day after admission. A number 24 F. cystoscope was easily passed through the urethra. The bladder urine was found to be very cloudy. The bladder was not irritable, and distended normally. The bladder mucous membrane showed some evidence of cystitis. There was no other bladder pathology evident. Both ureteral orifices were easily seen; the right seemed normal, the left somewhat reddened.

A No. 6 F. catheter passed readily to the right pelvis. There was no evidence of stasis in the pelvis or increased pelvic capacity. There was a normal pelvic flow of clear urine. Urine from this side showed a rare white blood cell and a few red blood cells, which were thought to be traumatic. No infection was demonstrable, either by stained

sediment or culture. The phthalein output by intravenous method was 30 per cent in fifteen minutes.

A No. 6 F. catheter passed readily through the left ureter but met obstruction near the pelvis. No urine was obtained from this catheter and there was no output of phthalein. A diagnosis of complete occlusion of the ureter by calculus was made.

Pyelography.—There was demonstrated a normal pelvis and ureter on the right side. No injection fluid reached the left pelvis on account of a large calculus which obstructed the flow from the ureter. Failure of renal shadow to appear in any of the films indicated probable destruction of the renal substance on the left.

Fig. 2. The calculus which was removed at operation. Note the cavities from which the cystin occlusions were removed.

Operation was performed the seventh day following admission. A left loin incision was made exposing an enlarged kidney which was tense, lobulated, grayish in color and showed marked induration of the perirenal and peripelvic fat. The lesion was evidently a calculous pyonephrosis with extensive destruction of the parenchyma. A nephrectomy was performed.

Pathological report.—Specimen consisted of kidney weighing 474 grams. The mass showed numerous lobulations which on pressure were found to be cystic cavities filled with fluid. The mass measured 15 by 9 by 5 cms.; 5 cms. of what appeared to be normal ureter was attached. On section the cysts were found to form the major portion of the mass. They communicated with each other freely and were filled with a cloudy fluid. A single large calculus blocked the pelvis

which was irregular in shape, hard in consistency, grey in color, and measured 3.5 by 1.5 by 1 cm.

Microscopic examination showed large areas which were atrophic plus extensive lymphocytic infiltration. The remaining glomerulæ and tubules were edematous and also showed cellular degeneration.

Diagnosis: Renal calculus, hydronephrosis, chronic inflammation.

Analysis of fragments from calculus showed the stone to consist of calcium and magnesium phosphates.

The patient made an uneventful convalescence during the first few days following nephrectomy, except for some gas distention which was easily handled. Eight days post-operatively he began to pass small particles of sand which attracted no particular attention in the laboratory and were not painful. On the eleventh postoperative day he ceased to void urine at all and complained of colicky pains in the right kidney region.

On the assumption that he had passed an overlooked ureteral calculus into his ureter a second cystoscopy was done. No obstruction to the passage of a No. 6 catheter through the ureter was noted but on reaching the pelvis about 15 c.c. of slightly blood-stained concentrated urine was evacuated rapidly after which normal pelvic flow was resumed. X-ray plates showed no stone. After cystoscopy the patient voided freely, the urine became clear, and the only abnormality noted was the presence of "sand" in the urine in the first voiding. Normal voiding continued for two days when obstruction again took place. A third cystoscopy was done. The ureter now appeared as red and edematous. A No. 7 and a No. 6 catheter were passed side by side up the ureter to the pelvis without meeting obstruction. It was assumed that the ureter was free. In spite of this procedure there was no relief afforded. The little urine obtained showed that infection was now present. Pyelotomy for drainage was decided upon.

Upon second operation, a large, tense, but otherwise normal looking, kidney was exposed. The pelvis was distended and firmer than normal fluid distention. When the pelvis was opened the pelvis was found to contain a little concentrated urine but the greater portion of the distention was found to be due to fine, sharp crystal, light colored sand. Cystin stone was first recognized at this time. The pelvic incision was left open and tube drainage placed.

The pathologist reported that the sand was both morphologically and chemically cystein crystals.

A re-examination of the stone from the opposite kidney showed an occlusion of cystein stone imbedded in the mixed phosphate calculus.

Convalescence from the second operation was stormy for the first few days. Drainage from the kidney was satisfactory and the wound closed in two weeks. Treatment employed was alkalization of the urine with sodium bicarbonate and the administration of a vegetable diet eliminating meat and fish and supplying protein in the form of

milk and eggs. The recovery seems to have been complete. Subsequent clinical study of the case has shown that the patient remains free of cystein crystals on increasingly liberal diet.

It appears that following nephrectomy, due to the loss of the stone-bearing kidney and probably to disturbed physiology from unknown factors, an accentuated cystein stone-forming tendency was transferred to a kidney which had previously shown no symptoms.

DR. HUGH H. YOUNG: Our time is limited, and I will confine myself to Dr. Quinby's paper, which I have enjoyed very much. An important complication following nephrolithotomy is fat replacement. In one of my cases, in which a stone was removed through a long cortical incision that was closed in the usual way by mattress sutures of catgut, the patient returned several years later with a recurrent calculus in the kidney which we found completely replaced by fat. There was hardly a trace of renal tissue to be seen, as you will see in the lantern slide.

Fat replacement, which has received very little attention in the literature, has accompanied renal calculus in four of my cases. The fatty area was small in one case and considerable in the others. It has also occurred in pyelonephritis in four cases, and previous reports in the literature have been accompanied by the assertion that fat replacement, or renal lipomatosis, occurs only in the presence of stone or infection of the kidney. I have one case, however, in which neither of these was present. The patient had suffered for many years with pain in the kidney. The x-rays showed the pelvis markedly compressed and a tentative diagnosis of renal tumor, involving the pelvis, was made. At operation I came down upon a marked fibrotic layer of fat surrounding the kidney and the pedicle. Fat followed the renal vessels and pelvis into the kidney through the hilus, greatly compressing the infundibula and calices, and interposing itself between the cortex and mucosa. It was always accompanied by a capsule, and eventually led to complete destruction or compression of the renal cortex.

On account of the danger of fat replacement following deep wounds through the kidney cortex and multiple mattress sutures, I think it desirable either to remove the stone through the pelvis, or to do as conservative an operation as possible through the renal parenchyma. Where the stone is located in a single calix, resection of this area so as radically to remove the stone and the stone-bearing area has been my practice for a number of years.

DR. HENRY G. BUGBEE: I would like to report a case of cystin calculi in a girl sixteen years of age. This girl was seen in 1930. She entered the hospital with a temperature of 104, and all the physical signs, symptoms and urological findings of a bilateral pyelonephritis. The urine from both kidneys contained pus cells and colon bacilli, and on the right side there was a marked diminution of kidney function. Cystin crystals were found in the urine from the right kidney, but the urine from the left kidney showed no crystals.

Following the manipulation incident to the cystoscopic examination, she passed four small calculi which were found to be pure cystin calculi. As the infection in the right kidney did not clear up and the function was persistently low, the kidney was removed. The kidney contained a large number of calculi, which were pure cystin.

We have followed this patient since operation over a period of three years, and we have found no cystin crystals in her urine since that time, nor is there a family history of cystinuria.

I would like to mention two cases of bilateral calculi, which illustrate several interesting points, both under my care at the present time. One is a woman who gave a history of no pain whatever, nor did she ever have any urinary symptoms. After a long motor ride, she passed some blood in the urine. She went to her family physician who had an x-ray taken which showed a calculus in both kidneys.

Symptomless calculi are seen from time to time; they are usually large or branching calculi, but these were not large. The calculus on the right side was about 2 cm. long and 1.5 cm. in diameter. The one on the left side was round and about 2.5 cm. in diameter. Both calculi could engage at the ureteropelvic junction, and an intravenous urogram showed well-marked back pressure on both sides, and a left hydronephrosis. I removed the calculi at two operations with an interval of three weeks.

The second case was a man who entered the hospital three weeks ago with a history that he had passed no urine for five days. An x-ray showed a calculus impacted at the right ureteropelvic junction. He was profoundly uremic. A catheter was passed up the right ureter, and by manipulation and water pressure exerted with a syringe attached to the catheter, the stone was dislodged and

there was a spurt of urine from the catheter. A large amount of urine was immediately passed through the catheter and the patient also voided alongside the catheter.

The diagnosis was made of reflex anuria on the left side with impacted calculus on the right.

Subsequently pain disappeared on the right side and the patient then complained of pain on the left side. The plain x-ray showed nothing on the left side, but intravenous urogram revealed a functionless kidney on this side. The pain persisted. Later, after a thorough clearing out of the intestinal tract, we were able to palpate a large mass in the left kidney region. As his temperature persisted, we did a left nephrostomy, incising a large pyonephrosis. Further study of the x-ray films showed two very minute shadows in the left ureter which could not be visualized in the first film. With a clear picture of obstruction on one side, one should make a diagnosis of reflex anuria on the other side with reservation, and not until every possible means of diagnosis has been carried out to exclude bilateral obstruction.

DR. HOWARD JECK (New York City): I think Dr. Stevens should be commended for coming out in open meeting and taking a stand against the time-honored custom of operating on the so-called better kidney first in cases of bilateral renal calculi. I should like to add to his reasons for not operating always on the better kidney, that we have no guarantee that the kidney which we do operate upon may not have to be removed during or shortly after the operation. During the operation uncontrollable hemorrhage may possibly necessitate the kidney's removal. After the operation, some such thing as acute suppurative nephritis may develop and render nephrectomy imperative. Either eventuality is the more likely to happen if during the operation for stone, it should become necessary to incise the renal parenchyma.

DR. CHARLES M. MCKENNA (Chicago, Ill.): I was intensely interested in both Dr. Stevens' and Dr. Quinby's papers. First of all, I think all bilateral renal calculi should be pyelogrammed and functioned. I might add that this holds true when we are dealing with a unilateral stone as well. One never knows when he is dealing with a poorly functioning kidney on the opposite side.

I agree with Dr. Stevens in operating on the kidney with the

poorest function first. I think the age of the patient should have something to do in the management before operating. To me it is always a problem and a great question whether to operate on those patients suffering with bilateral silent stones, especially when the patient is having no symptoms other than running pus in the urine.

I think Dr. Young hit the nail on the head when he brought out the subject of lipomatosis. We have had three cases of the type Dr. Young mentioned. I might add that they were all in women; they were all fleshy and the youngest was thirty-eight years of age. Each case ran considerable pus before operation, and in those three cases a fibro-lipomatosis formed after the removal of the stone. The kidney had to be removed subsequently.

Now the question in my mind, when we are dealing with a bilateral calculus, and by that I mean of the staghorn type, is this: Is one justified in removing the stone when the patient is having no disturbance? But it is easy enough to visualize when we have a fibro-lipomatosis on one side that it might develop on both sides. We believe the pre-operative care is very important in renal bilateral calculi. We have gone so far as to irrigate the kidney pelvis on both sides and keep them under observation until such time as we believe them to be in the best possible condition before operating. I think Dr. Stevens' paper is one that deserves a great deal of consideration.

DR. G. R. LIVERMORE (Memphis, Tenn.): I would like to report a case of cystinuria with rapid stone formation, in a child five years of age from Alabama. Dr. Young removed a stone from the ureteropelvic junction of this child about six or eight months before I saw him. When he came to me, there were probably fifteen or sixteen small stones in all, one about an inch in length and many smaller ones. These stones had formed within the six or eight months' period from the time Dr. Young had operated on the other side, which, incidentally, showed no stone at that time.

We have been told about alkalinization in such cases, and Dr. Crowell reported some cases of cystin stones that had disappeared under marked alkalinization of the urine. This child had been kept on marked alkalinization and sulphur-free diet since operated on, and yet these stones had formed within six or eight months. I removed the stones by pyelotomy and succeeded in getting all of

the fragments of stone from the calices of this kidney as demonstrated by an x-ray plate.

This child returned home. It was in September that I operated. He came back to me in February when Dr. Randall, who happened to be in Memphis, saw this case with me. The child then had a stone probably almost an inch in length which had reformed in the pelvis of the left kidney. That was from September until February that this large stone had formed in the pelvis of that kidney from which I had removed the previous stone probably an inch in length. This child has been constantly alkalinized and constantly on a sulphur-free diet. Dr. Randall suggested that we try irrigation of the pelvis of the kidney with an alkali. We used ammonium hydroxide one-tenth of one per cent and later increased to one-half of one per cent. With constant irrigation for thirty-six hours, and with the child also taking alkali by mouth, there was absolutely no effect produced upon the stone.

I think the theory of alkalinization as being the means of preventing cystin stones, as proved in this case, is incorrect. I am convinced faulty metabolism is responsible for the formation of cystin stones, and we must correct the defect in metabolism in order to prevent their reformation.

DR. V. J. O'CONOR (Chicago, Ill.): I am very much interested in Dr. Randall's remarks concerning the large number of calcium carbonate stones which his type of analysis shows to be in a more or less pure state. The calcium carbonate stone is said to be a very rare one in the usual textbook on this subject. In our part of the country, many of our medical men have for a number of years treated gastric and duodenal ulcer patients by the Sippy method. This entails the ingestion over a long period of time of large quantities of heavy calcined magnesia and is supplemented by various bismuth and chalk powders.

In 1920, in consultation with Dr. Sippy, I saw one of his patients in acute renal colic. After ureteral dilatation, this patient passed a snowy white, rough stone from the ureter and this stone on analysis showed pure calcium carbonate salt. At that time I suggested that the alkaline management, upon which this patient had been for eight or nine years, might have had some bearing on the development of this stone, because a complete study of the

patient showed no evidence of urinary tract infection and no stasis in the ureter or kidney pelvis.

Since 1920, I have seen thirty-eight patients who have presented exactly this same clinical picture, that is, no evidence of urinary obstruction, no urinary infection, but who have been on so-called ulcer management with large doses of alkali for varying periods, and who have passed either spontaneously or after instrumentation, white, rough, calcium carbonate stones. Only one patient required operation to remove the stone, and the other thirty-seven passed something over 100 stones.

The interesting thing to me in these patients is that they all had a distinctly alkaline urine, that the character of the stones when passed was identical, and that they either had a preponderance of calcium carbonate salt in them or were composed of almost pure salt. After these stones dried out, it was characteristic of them that they disintegrated on the slightest pressure into the finest type of powder.

Two of these patients are interesting enough to go into some detail in this regard. A man of fifty, who had been operated on several times for gastric ulcer without relief, has been followed for ten years, during which time he has been able to keep comfortable only on Sippy management. During these ten years, he has passed sixteen stones, each of which was accompanied by terrific colic, but with complete cessation of symptoms until the succeeding attack. Urologically there was no evidence of any reason for these stones. A year and a half ago the patient was placed on mucin treatment, and in line with the work of Dr. Higgins on alkalosis in these patients, I placed him on a modified acid-ash diet. The mucin controlled his ulcer symptoms, his urine has run slightly acid during this time, and he has not had an attack of renal colic in eighteen months.

Another patient, forty-two years of age, passed eighteen stones in a period of twelve years. He was also put on mucin for his ulcer and large quantities of haliver oil and Vitamin A were given over a period of two years. This patient also has slightly acid urine, but he has not had a stone form during this time.

I make these remarks purely as a clinical sidelight on the undoubted association of prolonged alkalinization with the formation of calcium carbonate stones. I do not think that we can explain

the formation of this type of calculus in this series of patients on any other basis.

DR. A. J. CROWELL (Charlotte, N. C.): I have nothing to add to what we have put on record with regard to cystin stone and cystinuria except to say I think it quite important that we know whether or not the stone is cystin. If so, recurrence is likely, following removal, and certainly, if preventive measures are neglected.

Just one remark with regard to Dr. Quinby's paper. It seems to me that the number of operations for the removal of ureteral stone, as reported by him, is rather large. I was surprised when he reported that he removes about 18 per cent by cystoscopic manipulation. We have removed, since we began this work in 1915, more than 800 by this method, and less than 18 per cent by ureterolithotomy. In the first place, there is no danger if removal is done by cystoscopic manipulation. We have not lost a single patient following their removal by this method, and I am sure the permanent results are equally as good as those following ureterolithotomy.

DR. ALEXANDER RANDALL: A man presented himself two years ago showing rather interesting symmetrical and equally placed stones in either ureter and having his pain primarily on the left side.

On the fifth day of March, 11931, a urogram was taken, again demonstrating the location of the stones and the very marked hydronephrosis back of them. I removed the left calculus by ureterolithotomy, and six weeks later the right by a similar operation.

Two months ago, having a twinge of pain in his left side and being fearful of his condition, the patient asked what to do and I suggested that the study be repeated. (Showing slide.) Here is a urogram taken two years and one day subsequent to the lower picture, showing what I think is the most remarkable return to normal and illustrating the marvelous comeback that nature can exert when once competent drainage has been established.

In regard to the cystinuria, we have been interested in it without much material. Having one cystin stone to work with, Dr. Beeson, who collaborates with me on this paper, took a hint from the analysis that we used to identify cystin and thought that possibly

sodium hydroxin would be a better solvent than others previously used. Working with Dr. Beck on the chemical side of it, they promptly showed that sodium hydroxin in very low dilution is just as competent as sodium hydroxid in a higher concentration.

Taking a fragment of a cystin stone about the size of a man's finger nail, he implanted it in a dog's left renal pelvis, and irrigating that pelvis over a period of six hours with a one hundredth of 1 per cent sodium hydroxid solution, succeeded—the dog was kept under anesthesia for that length of time—in proving a loss of 23 per cent by weight of that stone in that period of time. It is an ideal solvent with one or two exceptions. The first is that you must beware of its use through ureteral catheters, unless you use the roentgenographic catheter. We attempted the two-way catheter on the market, of the old brown variety, and I warn you that the weakest solution of sodium hydroxid will make that look like a strand of worsted in about twenty minutes. But it does not seem to affect the x-ray catheter.

Likewise it has no effect of detrimental character on the rubber ureteral catheter. But—and this is the crux I think of the whole thing, and I trust Dr. Sullivan will bear me out—it isn't a question of the solvent so much as the quantity of the solvent. The difficulty, I am sure, will lie more in providing some form of copious, constant irrigation rather than just the making of a solvent which we know in test tubes will dissolve cystin.

Dr. Howze has some very interesting x-rays of a case in which local therapy of a renal pelvis has demonstrated solvency of a calculus. I wonder if the floor may be granted him to present these plates.

DR. CHARLES P. HOWZE (Washington, D. C.): Dr. Randall has asked that I give you a brief history of this case in which the value of pelvic lavage with 1 per cent phosphoric acid is definitely demonstrable.

The patient is an Englishman, thirty-five years of age, who is a chronic stone former. In 1926 he had a vesical calculus which was removed by litholapaxy, and in 1931 a pelvio-lithotomy was done in Cleveland for a calculus in the left kidney. I first saw him one year later, with another stone filling the lower calix of the left kidney.

The voided urine was acid. The catheterized urine from the

right kidney was acid and showed no infection, while that of the left was alkaline and revealed 25 to 30 pus cells and innumerable bacilli to a microscopic field. The function of the two kidneys with phenolsulphonephthalein was equal and normal—15 per cent in fifteen minutes. The calculus was removed easily through a small nephrotomy incision, followed by a thorough lavage of the pelvis. Convalescence was uneventful and the patient was discharged from the hospital on the fourteenth day with the wound healed.

Two weeks later he had an attack of colic on the right and passed a small calculus. At this time the x-ray revealed an incrustation and mottled framework of a new calculus, again filling the lower calix of the left kidney. I then began pelvic lavage with 1 per cent phosphoric acid at five-day intervals. The urine from the kidney became acid to litmus following the second treatment and continued so. There was a complete disappearance of pus cells and a negative culture, following the fifth treatment. X-ray at this time revealed practically a complete disappearance of the shadow —there remaining only a small speck.

Unfortunately, the patient had to return to England after this treatment, taking the calculus with him. I hope, however, to obtain it in the near future for chemical analysis.

QUESTION: How long did you continue those lavages at each treatment?

DR. HOWZE: I distended the pelvis to the point of slight discomfort, then removed the catheter and had the patient sit up.

DR. ROGER C. GRAVES (Boston, Mass.): Dr. Kretschmer and Dr. Crabtree both introduced an important question clinically with reference to the cystin stone, and that is its visibility by x-ray. As a matter of fact, the situation I think is really quite definite. Where the cystin stone has an admixture of other salts which are opaque to the x-ray, the calculus, of course, will show, as in the case of Dr. Kretschmer's first patient. Where the stone is of pure cystin, it may or may not show in x-ray, so that we cannot depend on that evidence alone.

A number of years ago I had under observation eight cases of cystinuria in two generations of one family, and the patient who started the investigation was an individual with a pure cystin stone which did not show by x-ray. To throw further light on this

phase of the problem, I closely packed pure cystin into a paraffin-coated capsule and swallowed it, and found that it did not show in an x-ray photograph of the stomach region, which at that time was not due to the thickness of the abdominal wall. If the pure cystin stone is of a porous, spongy texture, as is very often the case, it may not show by x-ray. If, however, the molecules are very closely packed together in a very dense texture, then that stone can be visible by x-ray even though pure cystin.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): There are several problems which remain unsolved in the interesting subject of cystinuria. I have on several occasions examined the urine in close relatives of patients with cystin stones and have found cystinuria present. Both the mother and brother of a patient who had repeatedly formed cystin stones were found to have cystinuria, but never had passed a calculus or were aware of any renal trouble or any other trouble in the urinary tract. Careful examination was quite negative save for the cystinuria. It is evident that there must be another factor present in these cases to cause the production of calculus.

Another feature of interest is the fact that many patients with cystin stones do not have bilateral stones. I recall several patients with unilateral renal stone. This would suggest the presence of an anatomic factor in the kidney itself which would cause the deposit of crystals.

The dietary treatment seems to be of value in some cases, while in others it is apparently of no value.

I have used Dr. Randall's very interesting suggestion of phosphoric acid in the treatment of renal lithiasis in several cases. Although I have not had very much success in reducing the size of stone, I did succeed in removing bacterial infection in some cases. If the infection in cases of repeated stone formation can be controlled by means of phosphoric acid, that in itself is a distinct contribution in prevention of further stones.

DR. H. L. KRETSCHMER (Chicago): I think everybody agrees that this is a disease of metabolism and that not very much is known about it. It is my opinion that the problem should be attacked from the standpoint of metabolic study. The question of recurrence, of course, interests us in this type of stone as it does

in any other type, and there are cases reported, such as was the case reported by Dr. Livermore, in which after a few months, recurrence of rather large stones occurred in spite of very rigid dietetic management.

On the other hand, there are cases in the literature where no attempt has been made to control the diet or control the reaction of the urine, and it has been noted that the patients have no recurrence for many years. The fact that recurrences do not occur for so long a time, even without management, has led some investigators to make the statement that they do not follow routinely a set program, this being altogether unnecessary. Therefore, we have men on both sides of the fence.

Our first case, Dr. Graves, was a pure cystin stone and there was no infection.

Dr. Alexander R. Stevens: I would like to make one comment on Dr. Quinby's paper. I understood that he made the statement that there was more damage to the kidney caused by renal than by ureteral calculi. I am very much impressed with the importance of the factor of obstruction, and especially when accompanied by infection. I think we don't see more cases of marked damage to the kidney from ureteral calculi because most patients with ureteral calculi have pain symptoms which send them to the doctor, who will, or at least should, see to it that the stones are gotten out, either through the normal channels or by surgery.

The stones in the kidney that are not obstructing (that are in a calix) will cause damage only as they grow, and somewhat in proportion to that growth. If a stone is in a calix, is not causing any pain, and is not accompanied by infection, I think it can perfectly well be left alone. Take periodic x-rays and operate only if the stone grows.

Dr. McKenna spoke of the importance of pyelograms. I think in all cases of calculi of the urinary tract we should have complete urograms. The exact location of a calculus is, according to my view, our most important guide in determining the treatment.

Dr. William C. Quinby (Boston, Mass.): I wish to thank the members for their very liberal discussion.

Kidneys containing new-formed fat form a definite group and a very interesting one, one about which I doubt whether we will be

able to learn much more than what we see clinically and pathologically until we know more about fat metabolism. The fat has been analyzed. It has special characteristics. It is doubly refractive and thus is called anisotropic fat. It occurs at times in kidneys bearing stones. In certain instances in which the infection is due to tuberculosis, portions of the kidney previously infected become infiltrated with this special type of fat. When this condition is marked, as Dr. Young has pointed out, a nephrectomy may be necessary. I doubt, however, whether one can make the diagnosis until at operation the condition of fatty metamorphosis is found.

Answering Dr. Crowell's remark about the small number of patients bearing ureteral calculus which we treated by intravesical manipulation, I feel that our number was possibly somewhat greater than it might wisely have been. The manipulative method of removing stones from the ureter is one which is accompanied by very real dangers, especially if the kidney above the stone be infected.

I should like to ask Dr. Crowell how many patients of those whom he has relieved by intra-ureteral manipulation have been examined at a period from three to five years afterward; in how many of these has he made cultures of the urine; and in how many cases has he found stones recurrent on such follow-up examination?

DR. A. J. CROWELL (Charlotte, N. C.): In reply to Dr. Quinby's question with regard to results obtained in the removal of ureteral stone by cystoscopic manipulation, I would say we have not made an analysis of this work since March 15, 1930, at which time Dr. Claude B. Squires of our clinic (*The Journal of Urology*, Vol. XXIV, No. 5, November, 1930) reported 606 cases of ureteral calculi, 528 of which had been removed by cystoscopic manipulation and forty-four by open operation. We advised open operation in twelve cases in which the patients did not return and in this group several were sent in for diagnosis only. In twenty-two instances the stone was not recovered but in a good proportion of these the calculi must have been passed following treatment, else the patient would have returned.

THIRD DAY, MAY 10, 1933

RENAL INFECTION DUE TO DILATATION OF A SINGLE CALIX

GEORGE GILBERT SMITH, M.D.

Boston, Massachusetts

Dilatation of a single calix due to ulceration or to stone formation is not uncommon. Dilatation of another type, two cases of which are to be reported, is far less frequent. No case of this kind is shown either in Hugh Young and Walters' "Urological Roentgenology" or in Braasch's "Urography." In such a case, the condition appears to be due to extreme narrowing of the infundibulum of a single calix. This contraction of the infundibulum is probably due to inflammatory tissue which has been deposited along the course of the communicating channel between the calix and the pelvis.

Case 1.—The first case was that of a woman of forty-nine; one month before entering the hospital (April 15, 1927) she had an attack of "cystitis" which lasted one week. This was followed by an attack of fever, nausea and pain in the left flank which lasted four or five days. The patient stayed in bed for two weeks. The day before entrance, she experienced very severe pain in the left flank; this became less acute and persisted as a dull ache. Her past history was unimportant. Examination showed an obese, healthy appearing woman. The right kidney was not palpable, the left kidney was definitely enlarged, smooth and tender. At cystoscopy, the bladder appeared normal. The left ureter was catheterized easily; the first 3 or 4 centimeters of urine obtained were thick and purulent; that which drained later was less cloudy. A pyelogram showed only the two lower calices. During the next two weeks the patient's condition improved. The temperature became normal and the kidney less tender, but nevertheless it remained considerably enlarged. At cystoscopy on April 30, both ureters were catheterized. Clear urine was obtained from the right side, hazy urine from the left. A culture of the bladder urine showed B. coli. (A guinea pig inoculated with urine from the left kidney showed no tuberculosis.) A phthalein test showed an appearance time of three minutes on the right, five minutes on the left. In twenty minutes, 20 per cent was excreted by the right

kidney, 10 per cent by the left. A pyelogram of the left kidney (Fig. 1) showed an essentially normal pelvis, and an oval cavity occupying the middle third of the renal cortex. A narrow connection could be seen between this cavity and the pelvis.

It seemed clear that the kidney infection would never clear up while this poorly drained cavity existed, so nephrectomy was done on May

Fig. 1. Case 1. Abscess of middle calix.

3. The kidney was surrounded by inflammatory tissue and on palpation felt irregular, with areas of cortical softening. On section after removal, the kidney showed in the center of the cortex a thick-walled pocket containing about 1 ounce of thick yellow pus. The pelvic mucosa was coated with fibrinous exudate. The renal tissue which remained appeared normal. Microscopic examination showed the cortex and medulla filled with fluid exudate and wandering cells. The pathologist's diagnosis was chronic suppurative nephritis.

Convalescence was uneventful except for slight sepsis in the wound.

Case 2.—The second case was that of a college student, a girl of twenty-one, whom I saw first February 10, 1933. In November, 1931, she had her appendix and a cystic ovary removed. Following her operation, she developed a urinary infection which has persisted, with exacerbations, to the present time. Her chief symptoms were attacks of fever, pain in the left kidney region, frequency and urgency of

urination. For two years she had been taking caprokol. Her past history was unimportant.

Examination showed no renal enlargement or tenderness. The urine was cloudy, 1020 specific gravity, slightest possible trace of albumin, no sugar, fifteen to twenty pus cells and one to three red blood cells per field, and many bacteria. Cystoscopy showed a normal bladder. At this time all urines were clear and showed no pus.

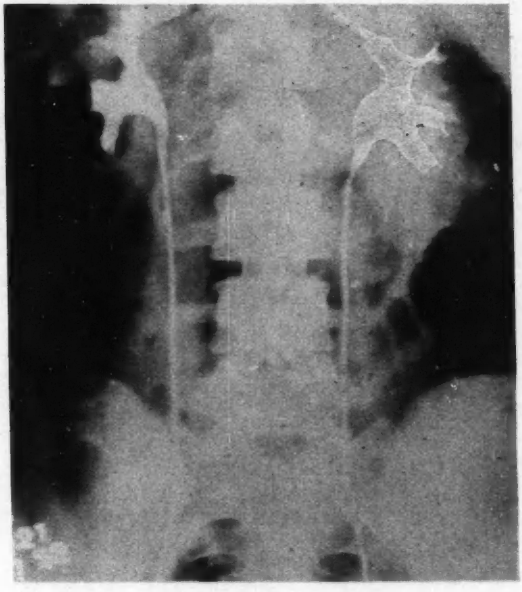

Fig. 2. Case 2. Dilated calix filled with sodium iodide solution.

Pyelograms showed a normal pelvis on the right. The pelvis of the left kidney was normal, but in the center of the renal cortex was a round shadow, not shown in plain x-ray films, which was interpreted as a dilated calix with almost complete obliteration of the infundibulum (Fig. 2). On March 8, 1933, the left kidney was exposed. It appeared to be normal except for a depressed area about 1.5 centimeters in diameter in the middle third of the cortex. This area was incised exposing a spherical cavity lined with apparently normal mucosa. At the bottom of the cavity, a dimple represented the opening of the infundibulum. A probe would not pass through this channel, and yet it was through this that the iodide had entered the cavity.

The cortex over this area was about 1 millimeter in thickness. The lining of the cavity was electrocoagulated and a cigarette wick packed into it. The kidney was fastened to the abdominal wall by one through-and-through silkworm-gut suture.

The wick was removed seven days after operation and the incision healed without ever having leaked urine. The patient's pain was entirely relieved and her urine contained no pus or bacteria when it was

Fig. 3. Dilated calix caused by pressure from renal tumor.

examined four weeks after operation. It seems probable that the poorly drained calix was the focus from which recurring attacks of pyelonephritis were initiated.

In the preceding two cases the pyelograms showed dilated and insufficiently drained calices which were the cause of the renal infection. That a similar condition may be due to the presence of a tumor is proved by a third case (Fig. 3), the pyelogram of which closely resembled those of Cases 1 and 2. In Case 3, however, the lengthening of the infundibulum gave the clue to the diagnosis.

In Cases 1 and 2, the decreased length of the infundibulum ruled out tumor as the cause of the obstruction. In these two cases the contraction of the infundibulum appeared to be constant and due to an inflammatory process. Harris and Harris[1] report two cases with dilatation of single calices which they discovered by pyeloscopy. These calices did not empty for twenty minutes. This condition was attributed by the writers to spasm of the muscle which surrounds the infundibulum.

SUMMARY

Two cases are presented in which narrowing of the infundibulum of a single calix resulted in dilatation and persistent infection of that calix. Infection of the kidney in one case and of the pelvis in the other resulted from these poorly drained calices.

REFERENCE

1. Harris, S. H., and Harris, R. G. S.: Renal sympathetico—Tonus and renal sympathectomy. Can. Med. Asso. Jour. (February), 1931, 24:235.

THE LONE KIDNEY IN PREGNANCY

GEORGE C. PRATHER, M.D. (by invitation), and E. GRANVILLE CRABTREE, M.D.

From the Urological Service of the Boston Lying-In Hospital Boston, Massachusetts

During the past several years, the Urological Service at the Boston Lying-In Hospital, has been asked to see the nephrectomized women who are pregnant and accept responsibility for the remaining kidney. After delivery the question also arises as to whether or not such a patient should take the risk of another pregnancy. We believe the urologist should assume the responsibility for these decisions, for he should be able to judge both anatomically and physiologically, how close to normal a kidney is under a given set of conditions. Moreover, this responsibility does not end with the delivery. If the cost of the completed pregnancy is a permanently damaged kidney, which will be a constant factor in this patient's life in the form of poor health, it is fair to say that possibly protection for the kidney under consideration has been neglected.

If one may refer to the obsolete for an analogy it could be said that we must regard the lone kidney as a permanent investment rather than a speculation for the duration of the pregnancy and therefore must protect the principal (the kidney) by the most conservative opinion. Fortunately, as will be shown, most lone kidneys carry on their work efficiently and with adequate reserve, but of course that should not diminish our watchfulness in discovering those which do need protection.

It is possible to get a reasonably accurate estimate of the ability of a kidney by clinical studies which include the laboratory and x-ray. This has been done on thirteen patients with lone kidneys during the past two and one-half years either during their pregnancy or relatively soon afterward. They represent a total of twenty-eight pregnancies.

STATISTICS ON REPORTED CASES

Evidence in relation to these patients has been reported in articles, the first of which was published in 1896. At that time Schramm described a patient who went through pregnancy success-

TABLE I

Case No.	Age	Para	Time of Nephrectomy	Pregnancies with Lone Kidney	Complications Previous Pregnancy	Complications This Pregnancy Advice
M. K. 1	20	IV	1928—3 yrs. ago Left hydronephrosis	1—1929 Present one due 1-12-31	None	None Continue
M. K. 2	21	V	1928—4 yrs. ago Left hydronephrosis	1—1929 1—1931 Present one due 6-12-32	None	None Continue
C. M. 3	35	VI	1927—3 yrs. ago Right Calculus pyonephrosis	None Present one due 4-15-30	None	None Continue
T. S. 4	26	III	1924—6 yrs. ago Rt. Tuberculosis	1—1928 1 miscarriage Present one due 4-11-30	None except miscarriage	Frequency Dysuria—loss of weight Therapeutic Abortion 12-18-29
G. I. 5	38	III	1917—14 yrs. ago Left Tuberculosis	1—1924 Present one due 7-16-31	None	None Continue
R. A. 6	25	II	1923—9 yrs. ago Rt. tuberculosis 1925—? Bilateral	1—1930 Present one due 8-26-32	Very irritable bladder Early Caesarian	Intense frequency—dysuria pyuria Therapeutic Abortion 1-25-32
D. M. 7	20	III	1922—8 yrs. ago Left ruptured	1—1928 1—1930 Present one due 10-6-31	None	None Continue
J. R. 8	31	II	1930—1 yr. ago Rt. Calculi Perineph abscess	0 Present one due 7-20-32	None	RBC—WBC in sed H. T. Albumin in 4th mo. Very Obese Interruption 2-17-32
C. S. 9	35	VIII	1926—6 yrs. ago Left pyonephrosis	4 miscarriages Present one due ? 8-30-32	Spontaneous Miscarriages	Miscarriage 3-16-32
G. A. 10	26	II	1926—6 yrs. ago Rt. pyonephrosis	1—1929 Present one due 5-29-32	None	Mild urinary tract infection Continue
M. A. 11	22	I	1927—5 yrs. ago Rt. ? diagnosis	0 Present one due 11-1932	0	Left hydronephrosis Interruption Explore kidney
S. 12	35	II	Congenital lone Kidney	1—1925 1—1927	None	
R. L. 13	23	IV	1929—4 yrs. ago Left cal. pyoneph	1—1929 1—1931 Present one due 2-27-33	None	None

Urine		Blood Pressure N. P. N.			Baby	Pyelogram during Pregnancy	Pyelogram after Pregnancy
Albumin	Sediment	During Pregnancy	After Pregnancy	2 Hr. Phthalein			
000 000 000	Negative	68/40 100/60 27**	110/78		Normal	10-7-30 Fig. 1 A***	4-16-31 Fig. 1 B***
000 000 000	Negative 2—3 WBC*	106/70 92/54 25**	120/70 39**		Normal	11-30-31 Fig. 2 A***	3-7-33 Fig. 2 B***
000 000 000	Negative Occasional WBC 2—5 WBC*	102/70 118/70	140/		Normal	None	7-23-30 Fig. 3***
000 S.T. At 5th	WBC and RBC* WBC and Casts Month	104/80 24**	116/70	39%	0	None	6-20-30 No filling
000 000 000	Negative Negative Negative	102/58 126/80 31**	114/70 33**	80%	Normal	2-5-31 Fig. 4 A***	11-12-31 9-20-32 Fig. 4 B & C***
S.P.T.S.T.	10—15 WBC* Loaded WBC ? Tbc. Bacilli on stain	122/70 32-33**	114/76		0	1-19-32 Fig. 5***	None
000 000 000	Negative Negative Negative	120/80 126/80			Normal	6-23-31 Fig. 6***	None
00T H. T.	Negative RBC-WBC*	100/70 25**		80%	0	None	5-6-31 (Before preg.) Fig. 7***
000 0	Negative Negative	120/70 122/70 30**		20%	0	2-4-32 Fig. 8***	None
000 000 00 V. S. T.	3—4 WBC* 10 WBC 20 WBC*	110/80 122/80 25-27**	114/56	55%	Normal	12-9-31 Fig. 9 A***	9-27-32 Fig. 9 B***
000 0	Negative Negative	116/68 25**	122/76	40%	0	5-4-32 Fig. 10 A***	10-13-32 Fig. 10 B***
S. P. T.	25 WBC*	33**		30%			2-19-33 Fig. 11***
00	Negative	122/70 140/88 30		30%	Normal		3-11-33 Fig. 12***

*—cells per high power field
**—mg. per 100 c.c. blood
***—see corresponding pyelogram

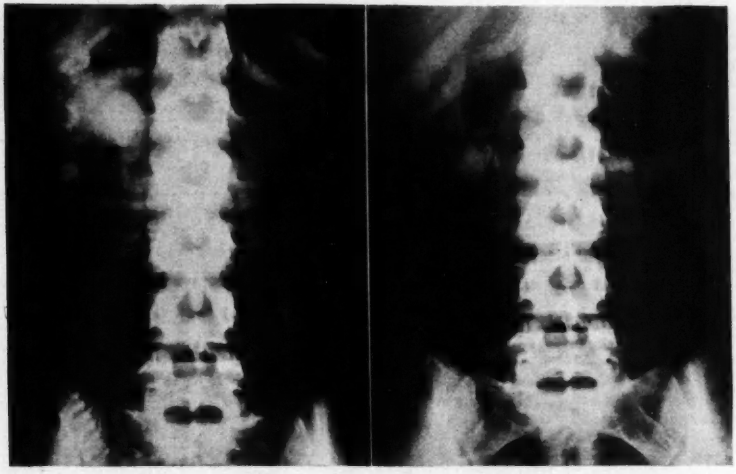

Fig. 1. Case 1. *A*, Intravenous pyelogram—six months pregnant. *B*, Intravenous pyelogram—right—three months post-partum.

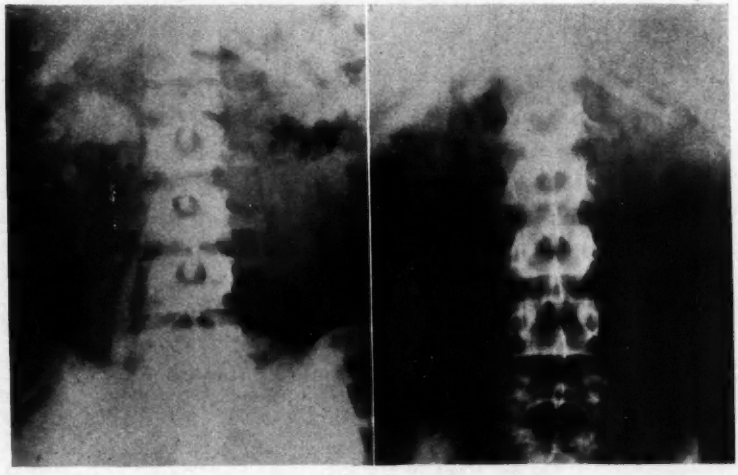

Fig. 2. Case 2. *A*, Intravenous pyelogram—right—two and one-half months pregnant. *B*, Intravenous pyelogram—right—nine months post-partum.

fully after having had a nephrectomy four years previously for hydronephrosis. Fritsch reported a miscarriage at six months following nephrectomy for ureteral fistula but the patient later had a child without complications. Israel accomplished a nephrectomy for tuberculosis in the fourth month without upsetting the pregnancy. In 1896, Tridonani also described a nephrectomized patient who went through three pregnancies successfully. Twynam and Maberly were the first English writers and added three cases.

TABLE III. CAUSES OF NEPHRECTOMY
Total number recorded cases 207

	No. Cases	Per Cent
Tuberculosis	113	55
Calculus Pyonephrosis	15	7
Hydronephrosis	8	4
Abscesses	8	4
Pyelonephritis	15	7
Infected Polycystic	2	1
Pyonephrosis	20	10
Calculi	18	9
Tumor	1	½
Ureteral Fistula	5	2
Traumatic	1	½
Congenital Absence	1	½

Bovee seems to be the first American writing on this subject, describing one case in 1902.

Numerous communications have been reported during the past thirty years, large series being recorded by Bleynie, Hartmann, Pousson and Matthews. In looking over all the reported cases it is frequently difficult to select accurately only the additional cases of a particular writer, thus avoiding a higher but inaccurate total number of cases and therefore destroying any statistical conclusions. As far as can be determined there have been 283 nephrectomized patients reported who have had 337 pregnancies. With our personal observations of thirteen women who have had twenty-eight pregnancies, there is a record of 296 nephrectomized women who have developed 365 pregnancies.

Cause of Nephrectomy.—These patients represent a group of young adults. It is at least interesting to note in 207 recorded instances that the cause of the nephrectomy in over half (55 per cent) has been tuberculosis. Pyonephrosis with the next highest

incidence represents 10 per cent and calculi 9 per cent. As seen in Table III, the reason for nephrectomy in this series represents many types of kidney pathology. Inasmuch as practically all of these patients are under thirty-five years of age it seems rather surprising, but true, that the principal indication for nephrectomy in young adult women is tuberculosis. This occurs five times more frequently than any other one cause.

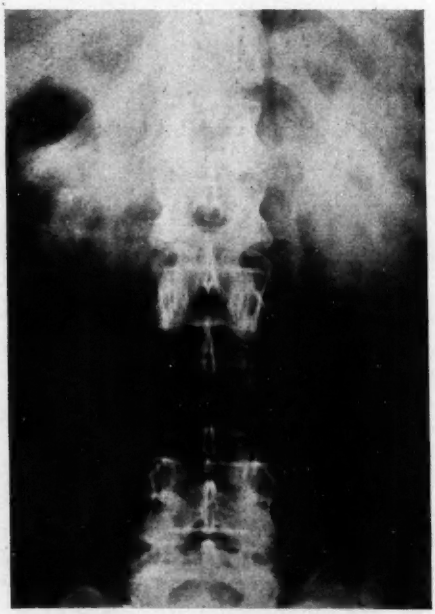

Fig. 3. Case 3. Intravenous pyelogram—left—three months post-partum.

Changes in Remaining Kidney After Nephrectomy.—Pousson in 1913 stated: "There exists only a very small number of histologic examinations of the remaining kidney, but all those which have been made show that the increase in volume relates less to the interstitial tissue than to the glandular tissue so that we have under consideration a condition of true hypertrophy." Pousson quotes Bonardi who studied the resistance of the remaining kidney to

infection in nephrectomized animals. Bonardi concluded that this resistance was notably diminished. Clinical evidence certainly does not support the latter statement as shown in Table IV which re-

TABLE IV. PYELITIS

	Patients—296 1.6%	Pregnancies—365 1.3%
Quoted by:		
Alexandroff		1 Post-partum
Brodhead		1 Pregnancy 7th mo.
Hall		1 Pregnancy 4th mo.
Mohler		1 Pregnancy 9th mo.
Prather		1 Pregnancy 9th mo.

TABLE V. MISCARRIAGES

	Patients—296 7.7%		Pregnancies—365 6.3%	
Quoted by:				
Cova	1		Israel	2
Cova	5		Pousson	7
Fritsch	1		Tuffier	1
Prather-Crabtree	6			

TABLE VI. TOXEMIAS

	Patients—296 2.7%		Pregnancies—365 2.2%	
Quoted by:				
Matthews	4		Morse	1
Mohler	1		Spencer	2

veals only a slightly higher incidence of pyelitis in pregnancy than is found in patients with two kidneys.

During pregnancy there seems to be little difference in the anatomic (mechanical) behavior of the lone kidney from those with two kidneys. The typical dilatation of upper ureter and kidney pelvis occurs with its associated kinks. This begins late in the third or early in the fourth month, as has been described previously by us. The lone kidney on the right side undergoes more dilatation than one on the left side. Slight rotation of the uterus during its enlargement produces more pressure on the pelvic portion of the right ureter than on the left. (Compare Figure 4*A* with Figure 9*A*). This inequality of dilatation would seem to indicate, as has been stated before, that the dilatation is secondary to pressure of the uterus at the brim of the true bony pelvis rather than any hyperplasia at the uretero-vesical junction. The mid-ureters

Fig. 4. Case 5. A, Intravenous pyelogram—four months pregnant. *B*, Intravenous pyelogram—four months post-partum. *C*, Intravenous pyelogram—right—fourteen months post-partum.

are carried laterally by the uterine enlargement just the same as when two kidneys are present.

From a physiologic standpoint the lone kidney which is not diseased maintains its excretory function during pregnancy in a splendid manner. Observations on catheter specimens indicate no disturbance that can be detected by the usual examinations for albumin, sugar, specific gravity and the centrifuged sediment. Blood pressure has shown no change during pregnancy from read-

Fig. 5. Case 6. Intravenous pyelogram—left —six weeks pregnant.

ings in the same patient post-partum. The non-protein nitrogen seems to follow the standard set by two kidneys averaging slightly lower than is found in the non-pregnant. Phenolsulphonephthalein excretion by the two-hour and ten-minute test measures favorably with the total put out when both kidneys are present. These optimistic remarks concerning lone kidney physiology are general statements to which exceptions can readily be found. In other words,

complications do arise in these patients with lone kidneys as can be seen by the charts, thus occasionally making action imperative if one is to avoid serious situations.

TABLE VII. INTERRUPTIONS

	Patients—296 5.7%		Pregnancies—365 4.6%
Quoted by:			
Cova	3	Matthews	5
Israel	3	Spencer	2
Prather-Crabtree	4		

TABLE VIII. DEATHS

	Patients—296 1.4%	Pregnancies—365 1.09%	
Quoted by:			
Castaigne	1		Uremia
Cova	1		Uremia
Fergusson	1		Eclampsia
Shepard	1		Uremia

TABLE IX. MISCELLANEOUS COMPLICATIONS

Peripheral Edema	1	Alexandroff
Albuminuria	4	Prather-Crabtree
	1	Fergusson
	1	Schramm
Contracted Pelvis	1	Maberly
Ruptured Wound	1	Twynam
Intense Frequency and Dysuria	2	Prather-Crabtree
Hydronephrosis due to Aberrant Vessel	1	Prather-Crabtree

Statistics on Complications in the Recorded Cases.—In order to have some idea of the possible or probable complications in women who have had nephrectomy and are pregnant, it is necessary to tabulate these occurrences in percentages.

Miscarriages seem to occur in 6 per cent if figured on total number of pregnancies, or 8 per cent, basing calculations on the number of patients (Table V).

Toxemias, used in a very broad sense, have been recorded in 2.2 to 2.7 per cent. Most of these have occurred late in pregnancy and several have necessitated interruption (Table VI).

The percentage of interruptions in the total number of cases is small, 5 to 6 per cent (Table VII). However, if one should take Matthews' series of fifty labors and our series of twenty-eight labors, making a total of seventy-eight, we find nine interruptions or 11.5 per cent. Matthews' publication in 1921 and the present

one represent the only large series reported in the past twelve years during which time obstetrical patients have been studied intensively from a laboratory and x-ray standpoint. It would seem, therefore, that in the future, with more detailed study and emphasis on long range protection of the kidney, interruptions will be deemed advisable in a percentage of at least 11.5 or more.

Deaths have been mentioned in only four instances making a mortality percentage of 1.09 to 1.4. In three of these, uremia is given as the cause, and in one, eclampsia (Table VIII).

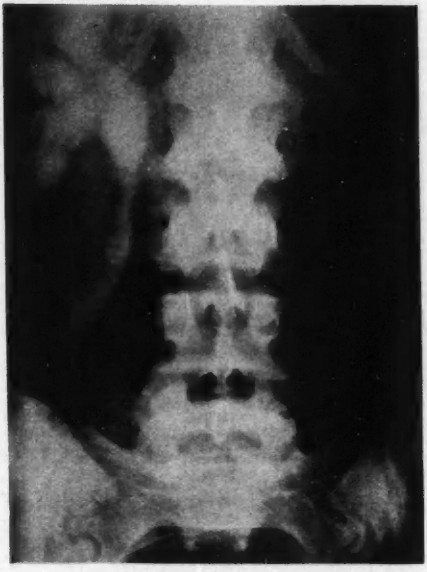

Fig. 6. Case 7. Intravenous pyelogram—right—five months pregnant.

Miscellaneous complications reported include peripheral edema, albuminuria, contracted pelvis, rupture of nephrectomy wound, intense frequency and dysuria due possibly to a legacy of urinary tuberculosis and hydronephrosis of the lone kidney caused by an aberrant vessel or fibrous band (Table IX).

The condition of the baby at birth is mentioned on 135 occasions,

the number alive being 115 and dead, twenty. These deaths include miscarriages and therapeutic abortions before a viable age.

In our series of cases no special form of anesthesia was used at the time of delivery. Most of them have had nitrous-oxide-oxygen and ether anesthesia. A few have had laparotomy and sterilization under that same anesthesia in addition to anesthesia at the

Fig. 7. Case 8. Intravenous pyelogram—left—interval between first and second pregnancies.

time of labor and none have had any suppression of urine or any known kidney damage.

ITEMS RECOMMENDED FOR STUDY

History of the pathology of the removed kidney is important to indicate whether the renal pathology is unilateral or bilateral. Since over half of the nephrectomies have been done for tuberculosis, one must determine if the remaining kidney shows any evidence of this condition. Guinea pig inoculations should always be done with such a history.

In addition to a thorough physical examination, detailed and repeated urine examinations, guinea pig inoculations of a catheter

specimen, kidney function tests and intravenous pyelography are indicated.

We believe that catheter specimens of urine should be used for examinations and we are convinced that there is no danger of repeated catheterizations in ambulatory patients if done with aseptic technic. Urine examinations including sediments examined under

Fig. 8. Case 9. Intravenous pyelogram—right—two and one-half months pregnant.

the high dry lens, are indicated every two to three weeks during the first six or seven months of pregnancy and each week during the last two months. Blood pressure observations are made at each visit.

Viewing the problem from a urologic standpoint, we have been satisfied to let the kidney function tests be represented by one of the nitrogen retention methods and by the two-hour phenolsulphonephthalein elimination test. These determinations are to be pre-

ferred early in pregnancy and can later be repeated to good advantage for comparison. While realizing that from an obstetrical viewpoint there can be serious renal dysfunction in the toxemias

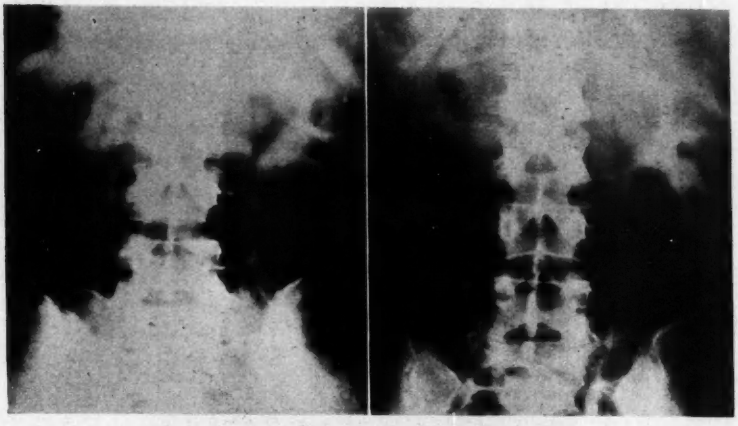

Fig. 9. Case 10. *A*, Intravenous pyelogram—left—three and one-half months pregnant (stone in stump of opposite ureter). *B*, Intravenous pyelogram—left—four months post-partum.

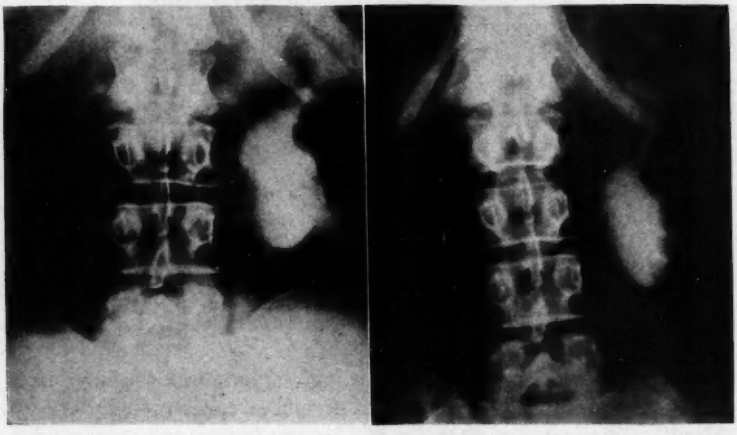

Fig. 10. Case 11. *A*, Intravenous pyelogram—left—three months pregnant. *B*, Intravenous pyelogram—left—five months after interruption of pregnancy.

with a normal blood urea nitrogen or non-protein nitrogen, we have felt that they should be used as routine until some improved method has become well established as a standard. Non-protein nitrogen readings from 24 to 35 mg. per 100 c.c. blood during pregnancy occurred in our series and were considered normal. Matthews reported blood urea nitrogen of 10.4 to 18 in three cases. The phenolsulphonephthalein test, perhaps, gives us a little more idea

Fig. 12. Case 13. Intravenous pyelogram—right—two years post-partum.

of the kidney reserve and is especially valuable as a supplement to the non-protein nitrogen or blood urea nitrogen.

We have not used the two-hour concentration examination routinely although it adds information in abnormal cases where added evidence of the renal status is desired.

Intravenous pyelography before the fourth month of pregnancy will give an accurate idea of any anatomic pathology existing prior to pregnancy. Even later in pregnancy one can obtain a reasonable idea regarding that point if familiar with the urinary tract changes in pregnancy. As stated in a previous publication, intravenous

pyelography in pregnancy gives satisfactory plates for diagnosis in 91 per cent and is without danger either to the mother or fetus.

By correlating the evidence obtained from these items in the study of the lone kidney in pregnancy, one can form a definite idea as to both the anatomic (or mechanical) status of this kidney as well as its physiologic efficiency. These facts combined with statistical data allow an accurate opinion concerning the kidney

Fig. 12. Case 13. Intravenous pyelogram—right—two weeks post-partum.

under discussion and a prognosis as to the safety of continuing the pregnancy.

OPINIONS PAST AND PRESENT

Schramm, who was the first to report on this subject, concluded that while pregnancy could go ahead without damage to the kidney, believed it advisable to prohibit marriage, fearing that it would be difficult to resist a toxemia or nephritis. Later, Ferguson suggested that marriage or pregnancy should be delayed for three years after nephrectomy to give the remaining kidney time to adapt itself to the double work. Raffin said, "One must look for albumin in the urine because sometimes the kidney which is left is suffering

with nephritis of which the seriousness is variable." In 1909 and 1910 Bleynie stated that conditions were favorable for the nephrectomized woman becoming pregnant. Pousson in 1911 said, "The preceding results must obviate fear of those who believe that a woman having had a nephrectomy cannot support the strain of maternity, but it does not mean that we should permit marriages in these cases with, for instance, the eyes closed. Before giving an opinion it is necessary to inquire into the general health and functioning of the cardiovascular system and the liver, factors of the greatest importance of the anatomic state and functioning of the remaining kidney." In 1911 Hartmann stated, "Many doctors fear to see pregnancy come to a woman who has had a renal operation, particularly a nephrectomy. Is this fear justified? Some of them believe it is, basing their fear on theoretical reasons. In fact, it is not demonstrated that the coefficient 'urotoxique' be augmented. It is, on the contrary, diminished during the course of pregnancy." Two years later after reviewing the subject again he concluded that the absence of one kidney did not appear to have any influence on the mortality rate in pregnancy. He noticed no change in lactation and did not believe that the absence of one kidney had any bearing on the abortions observed. In 1921 Matthews stated that if the nephrectomy had been done for tuberculosis, two to four years should elapse without re-appearance of symptoms before pregnancy should be allowed to take place. He quotes Israel, who held that pregnancy should never be allowed to progress after nephrectomy for renal malignancy.

On the basis of reported cases, particularly those of the French writers, 1909-1913, Matthews', and from our own series, the statement, "Nephrectomy is not a contra-indication to pregnancy," remains unchallenged. Definite exceptions exist, however, and it will only be by careful and adequate observations that the proper cases are allowed to continue their prenatal course. Thought and attention to the lone kidney in regard to the more distant future must be emphasized, as well as consideration for the duration of the pregnancy. The patient whose study reveals nothing abnormal has little to fear and should always be allowed to continue the pregnancy under close observation.

INDICATIONS FOR INTERRUPTIONS OF THE PREGNANCY

The indications for interruptions fall into two classes. First,

finding a definitely damaged kidney in the early part of pregnancy by one or more of the above items of study. In such a situation, continuing to the puerperal state might permanently cripple such a kidney, not to mention the danger of a renal breakdown sometime before delivery, with serious consequences to the mother. Second, finding a normal kidney in early pregnancy by all known methods of study, but in which case an obstetrical or renal complication develops later in pregnancy and which demands action to save life. Occasionally these lone kidney patients, like many obstetrical patients, are not seen until late in pregnancy or when in serious difficulties, possibly both.

Interruption, therefore, is an effective safety valve which should be used in lone kidney cases showing remnants of urinary tract tuberculosis, anatomical pathology which may result in irreparable damage from the added dilatation due to pregnancy, or in which kidney physiology is abnormal as shown by urine examinations and function tests.

CONCLUSIONS

1. In general, nephrectomy is not a contra-indication to pregnancy.
2. A total of 296 nephrectomized women who developed 365 pregnancies is recorded.
3. Tuberculosis has been the cause of the nephrectomy in 55 per cent of these patients.
4. Kidney pelves and upper ureters undergo the familiar type of dilatation during pregnancy. The rights show more dilatation than the lefts.
5. In a normal kidney, the function tests show an adequate margin of safety during pregnancy.
6. Items in the study of these patients should include thorough physical examination, repeated examinations of the catheter specimens of urine, guinea pig inoculation of urine specimen in patients with tuberculous urinary tract history, blood chemistry, two-hour phenolsulphonephthalein tests and intravenous pyelography.
7. Earliest writers advised against marriage or pregnancy for the nephrectomized woman.
8. Accumulated statistics indicate a mortality rate of only 1.09 to 1.4 per cent.
9. Patients showing no abnormalities in the items of study

should always be allowed to continue pregnancy under close observation.

10. Desire to avoid permanent kidney damage combined with closer study may, in the future, result in a somewhat higher percentage of interruptions of pregnancy.

11. Indications for interruption—

(a) finding a damaged kidney early in pregnancy;

(b) obstetrical or renal complications later in pregnancy.

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BACILLUS PROTEUS PYONEPHROSIS WITH BLOOD INFECTION

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH OPERATION AND RECOVERY

DAVID W. MacKENZIE, M.D.

Department of Urology, Royal Victoria Hospital, Montreal, Canada

Bacillus proteus infections of the urinary tract are comparatively common, and many more cases must be seen than are reported in the literature. The reported cases all seem to be associated with trauma, either instrumentative or operative. Kretschmer and Mason found twenty cases due to this organism in a series of 305 urinary infections. Eight of these were in pure culture and twelve were part of a mixed infection.

Hagar and Magath believed this organism to be the causative factor in encrusted cystitis, and found it in nine cases of vesical calculus. They were also able to cause an encrusted cystitis in rabbits by intravesical injections of B. proteus following trauma to the bladder.

Archer reported an interesting case of an acute pyelonephritis in which a pure culture of B. proteus was obtained from the right kidney.

Taylor has endeavored to work out the pathogenicity of B. proteus, and in thirty-one urinary strains thought that seventeen were pathogenic, four were doubtful and ten were not pathogenic. Eight of these were a mixed infection and he has classed these as not pathogenic. Of the fifty-three strains which he collected from all sources, he has given the following description:

"All the strains were bacilli with rounded ends, actively motile and consistently gram negative. The variability in length seemed to depend upon the conditions under which the strain was growing. The average length was from 2-4 u. Long filamentous bacilli up to 20 and 30 u. were found when a young culture was spreading rapidly.

"The youngest colonies on agar plates were often discretely round, clear and sharply defined; later these discrete colonies invariably spread outwards, either as a delicate aura, by fine finger-like processes

or as a uniform film. The amount of spread depended on the amount of moisture on the surface of the plate.

"Gelatine and inspissated blood serum were always liquified. All strains showed hemolysis.

"The sugar reactions were variable. Lactose, mannite and dulcite turned alkaline and no gas was formed. Dextrose showed acid and gas. Saccharose showed acid and gas in forty-nine strains. Four showed acid but no gas. Maltose was alkaline in fifty strains, but three formed acid and gas. These latter three strains showed indol formation. The other fifty strains produced no indol."

B. proteus occasionally enters the blood stream and causes general septicemia. These infections are not so frequently seen and are not necessarily fatal in their termination. A few have their original focus in the urinary tract, although many are in no way connected with it. Hicks found B. proteus in the blood stream of a patient with a suppurative ovarian cyst. This proved fatal and the same organism was found at autopsy in the primary focus and also in the spleen.

In a case of B. proteus septicemia following prostatectomy, Wallace and Dudgeon used an autogenous vaccine beginning with 15 million bacilli increasing to 500 million bacilli with ultimate recovery of the patient.

Kernan has described two cases of blood infection by B. proteus—one in which a peritonsillar abscess was the original focus; the second where an otitis media was the starting point. This latter case proved fatal. Irimonoiu and Popa reported a case which came to autopsy as typhoid fever. They found a suppurative otitis media complicated by a pulmonary abscess. B. proteus was recovered both from the spleen and the pulmonary abscess.

Warren and Lamb recorded a fatal case of B. proteus septicemia in a patient with myelogenous leukemia and tuberculosis.

Barrington and Wright in investigating the question of bacteriemia following operations upon the urethra found B. proteus in the blood stream in three cases in a series of twenty-three operations. All three patients made a complete recovery.

Kretschmer and Mason reported two cases of blood stream infection by B. proteus. Both of these were cases of renal calculus. In one, renal tuberculosis was also found and following nephrectomy recovery took place. The other case proved very interesting as B. proteus had been recovered from the urine some

months before septicemia developed, following catheterization of the ureter.

Walters and Scott had a case similar to that of Wallace and Dudgeon, a proteus septicemia following prostatectomy. They also mentioned having had a previous case, also with recovery.

Scott, in investigating the value of immediate blood cultures, at the time of the development of fever and chill following instrumentation or operation, found five B. proteus infections out of a total of eighty-two positive cultures. Three of these cases proved fatal.

Hyman and Edelman in a similar, though smaller, series found three B. proteus septicemias, one of which proved fatal.

Nakagawa reported the first case found in Japan, that of a patient with a cord bladder. Proteus bacilli were found in the blood, urine and feces during life.

The details of our own case are as follows:

C. W., aged forty-six, was admitted to the medical ward of the Royal Victoria Hospital on June 7, 1932, because of pain across the back, with chills and fever, of two weeks' duration.

The patient was in good health until caught in a rainstorm, while fishing in the Laurentians over the holiday on May 24. He felt perfectly well the next day, but on June 2 he developed a slight cough and had chilly sensations and vague pains all over his body. The following day the pain was dull and centered between the shoulder blades. He had a slight cough. He also noted pains in both legs and feet. That afternoon he developed a marked diarrhea which persisted for three days. At no time did he notice any blood or mucus in his stools.

He had fever each evening with accompanying chilly sensations, but had no definite chills. The pain in his back was accentuated on coughing. He had no urinary symptoms, nor pain in the lumbar region. On June 6 the diarrhea ceased, but the fever and pains in the back persisted.

Personal and family history were negative.

Physical examination on admission showed patient to be a white male of about stated age. Temperature was 100.4°; respirations 26; pulse 116. The examination of the head and neck showed nothing abnormal. There were no enlarged glands. The chest was emphysematous and resonant throughout. Breath sounds were vesicular in character except over each hilus, where the sounds were slightly harsh. No râles were heard.

The pulse was regular, rapid and of good volume. The heart was

within normal limits, the sounds distinct and clear. Blood pressure was 125 systolic and 78 diastolic.

The abdomen was rounded, symmetrical, moved well on respiration. There were no areas of tenderness or rigidity. The liver and spleen were not palpated.

There was no costo-lumbar tenderness. The kidneys were not palpated and there was no tenderness along the course of either ureter. The external genitalia were normal. The prostate was normal in size, shape and consistency.

On the skin over the left side of the abdomen and around the base of the left lung were scattered a few rose pink spots, raised, which faded on pressure.

The nervous system was normal.

The urinalysis on admission showed a clear amber urine, neutral, specific gravity 1020. A faint trace of albumin was present, but no sugar. There was an occasional white blood cell in the microscopic examination and a few epithelial cells.

The white blood count was 12,000. The patient was put upon routine typhoid orders. Subsequent examination of the stools was negative for typhoid bacilli. The Widal test was negative for typhoid *B* and paratyphoid *A* and *B*. Undulating fever was then suspected, but agglutination tests for B. abortus and B. melitensis were negative.

On June 18 the examination of the chest showed a slightly higher pitched note over the left inferior lobe, with some fine post-tussic crepitations. This was suggestive of a clearing patch of bronchopneumonia and he was treated for such a condition.

The x-ray of the chest was negative for consolidation or recent tuberculosis.

During all these weeks the patient was running an evening fever of about 101°, and on July 4 a blood culture was taken which was positive, B. proteus mirabilis. This was repeated on the 9th, with similar results.

It was noted then that scattered pus cells and bacilli were present in the urine. The urine was cultured and a pure growth of B. proteus was obtained. At this time the Department of Urology was called in consultation. The patient had been having an intermittent fever of from 100° to 101° daily for six weeks. He had lost considerable weight. The examination of the genito-urinary system showed some changes. There was slight costolumbar tenderness on the right side. The right kidney was easily palpated and was slightly tender. The lower pole of the left kidney was palpable but was not tender. The urinalysis now showed a definite trace of albumin with clumps of pus cells and many bacilli. The phenolphthalein test 1 c.c. intramuscularly showed the first hour 35 per cent, the second 20 per cent, a total for two hours of 55 per cent.

The blood count was hemoglobin 70 per cent; red blood cells, 3,500,000; white blood cells, 13,000. The blood creatinin was 1.27

mgms. per cent and the non-protein nitrogen was 20.7 mgms. per cent.

On cystoscopic examination the bladder mucosa was inflamed. The ureteral orifices were normal. The ureters were easily catheterized and specimens of urine obtained from each kidney.

	Right	Left
Macroscopic	hazy pale	clear pale
Volume	4 c.c.	8 c.c.
Urea, grms. per c.c.	.005	.045
Microscopic	Pus scattered, epithelial cells, bacilli	Occasional white blood cell. Epithelial cells.
Culture	B. proteus	No growth
Phenolphthalein test 1 c.c. intravenously		
Appearance time	0	3 mins.
% in 10 minutes	0	10%

X-rays showed a normal left kidney shadow and a large indistinct right kidney shadow. No calculi were seen. Pyelogram right, with 6 c.c. of sodium iodide 12 per cent, showed a dilated, distorted and irregular pelvis and calices.

Following cystoscopy the temperature fell for several days, then reappeared as before. The blood culture following cystoscopy was sterile, but in view of the marked infection of the kidney and the total absence of function from that side, nephrectomy was performed.

The report on the kidney from the pathological department stated: "A kidney about normal size with a large amount of perinephritic fat. The cut surface is pinkish gray. The differentiation between cortex and medulla is faintly visible. The pelvis is filled with clotted blood streaked with yellowish gray material. Microscopically the medullary portion of the kidney was extensively destroyed by fibroblastic tissue containing many leukocytes and pus cells. This exudate filled the stroma and extended throughout the cortex in linear patches. The glomeruli were swollen and disintegrated. The convoluted tubules contained many hyaline and granular casts."

Culture of the kidney tissue at operation showed a growth of B. proteus. The patient made a protracted but uneventful recovery. When seen seven months later, he had gained 30 pounds in weight and was able to carry on in his ordinary duties. Urinalysis then showed a faint trace of albumin and a few white cells. Proteus bacilli were still present in the urine. For the past several weeks he has been receiving injections of an autogenous vaccine starting with 50 million per injection and working up to 2000 million, so far, without any change in the urinary condition.

DISCUSSION

From what we have been able to find in the literature, it would seem that proteus bacillus infections are common in the urinary tract. Septicemia from this source is comparatively rare, only seventeen cases in addition to our own could be found. Of this number, five proved fatal. From sources elsewhere than in the urinary tract, five cases were reported, all of which proved fatal.

The main reason for reporting our case is that we believe it to be unique. The greater majority of the septicemias on record give some history of a primary urinary infection, some instrumentation or even operation, before the onset of the blood infection. We can find no case with a history or findings similar to our own. We believe that the onset of the infection closely followed the intestinal upset suffered by the patient while on a holiday. It may have been due to exposure, or the ingestion of contaminated food. Many outberaks of enteritis and dysentery have been traced to the ingestion of food contaminated by B. proteus.

Following the introduction of the bacillus into the blood stream there developed the typhoid-like symptoms, which masked the condition until the bacilli were found in the blood stream and the urine. Later the focus in the destroyed kidney was found and removed. We believe this focus to be secondary to the blood infection and not the original cause of it.

SUMMARY

1. A case of bacillus proteus septicemia with acute pyonephrosis and recovery has been reported.

2. The literature on B. proteus blood infections has been reviewed.

3. The characteristics of bacillus proteus are briefly discussed.

For the bacteriologic studies of this case we are indebted to Professor Murray and his associates, of the Department of Bacteriology, Royal Victoria Hospital.

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BACILLUS ALKALESCENS PYELONEPHRITIS WITH BLOOD INFECTION

REVIEW OF THE LITERATURE AND REPORT OF A CASE WITH RECOVERY

DAVID W. MacKENZIE, M.D.

Montreal, Canada

We are reporting the following case of Bacillus alkalescens pyelonephritis with septicemia, first, because of the rarity of the organism involved, and second, for its very extreme clinical interest.

We made a very careful search of the literature from the year 1916 to the present day, and were able to find only two other cases of pyelonephritis caused by the Bacillus alkalescens.

The first case was that reported by Smith and Fraser in 1928. The patient was four days post-partum when she suddenly developed chills and high fever. The Bacillus alkalescens was isolated repeatedly from the blood, stools, and even from the uterus. The authors do not mention whether there was any infection of the kidney. It is noted, however, that albuminuria was present. After a long convalescence the patient made an excellent recovery.

The second case was reported by Popoff and Spanswick in 1931. This patient developed all the signs and symptoms of an acute pyelitis of pregnancy in her third month. She had severe pain in the back and abdomen, frequency and dysuria, nausea and vomiting and high fever. Repeated cultures of the stool and urine were positive for the Bacillus alkalescens. Blood cultures, strangely enough, were always negative. These authors were able to demonstrate, however, agglutination of the patient's serum with the organisms isolated from the urine and stool up to a dilution of 1 in 640, thus showing that there were present specific antibodies in the patient's blood. This patient also made a good recovery after having had a therapeutic abortion. It is interesting to note that in both these cases there was a marked secondary anemia with icterus.

Before discussing our own case we shall briefly describe some of the characteristics of the Bacillus alkalescens.

The Bacillus alkalescens apparently belongs to the so-called atypical dysentery group and resembles Flexner's bacillus very closely. It differs from this latter organism in the fermentation of xylose, dulcite and rhamnose. The organism is a gram negative non-motile short bacillus. It produces acid without gas in glucose, maltose, mannite and dulcite media. Its action on litmus milk is characteristic; after a week or ten days it becomes blue with a strong alkaline reaction. In discussing the Bacillus alkalescens Andrews states that no case had been encountered in which this organism has been agglutinated by the serum of the patient from whom it has been isolated. This phenomenon was observed in the case that we are reporting. Popoff and Spanswick, on the other hand, were able to get agglutination on two occasions up to a dilution of 1 in 640.

The following is the record of the case we are reporting:

E. W., female, aged thirty-one years, was admitted to the Urological Service on July 14, 1932, complaining of pain in the right loin, chills and fever, frequency of urination, dysuria, nausea and vomiting, fatigue and loss of weight.

The history dated back to August, 1931, when the patient was suddenly seized with a severe stabbing pain in the region of the right kidney. This pain radiated downwards to the right hip. The attack lasted for about an hour and was then replaced by a dull pain in the right lumbar region, which was present for about one week. The patient had no other symptoms at that time. She was free from any discomfort until April, 1932, when she had a similar attack as mentioned above. This lasted for about three days.

Five days prior to admission (July 9, 1932) she began to be troubled with marked frequency of urination, dysuria and urgency. About the same time the pain in the right costolumbar region returned. These symptoms were associated with nausea and vomiting. She also had a number of severe chills associated with high fever. She was admitted to the service as a very sick patient.

She had the usual childhood diseases, and had one pregnancy, which ended in a miscarriage at the seventh month. Family history was irrelevant. On admission the patient appeared acutely ill. Her face was very flushed and her skin hot. She was well developed and nourished. Temperature was 102°, pulse 100 per minute, respirations 20 per minute. Eyes, ears and nose were normal. The throat was slightly engorged; tonsils not large. The thyroid was not enlarged. There were no abnormal enlargements in the lymphatic glands. Respiratory system was normal. Blood pressure was systolic 126, diastolic 68. Pulse was rapid, 100 per minute. Otherwise nothing abnormal was found.

The abdomen was rounded and moved freely on respiration. There were a few striæ present. There was marked tenderness in the right flank and the right lower quadrant of the abdomen. There was no rigidity anywhere. The spleen was enlarged and easily palpated. The edge of the liver was felt below the right costal margin.

The skin was hot; no rashes, no deformities of extremities, no edema present.

Pelvic examination was negative except for slight vaginal discharge and mild tenderness in the left fornix.

Kidneys showed marked tenderness in the right costolumbar angle, in the right flank and over the right kidney region in front. The right kidney was low and easily palpated. There was also slight tenderness in the left costolumbar angle. The left kidney was low and easily palpated. There was marked tenderness over the right lower quadrant of the abdomen. None on the left side. There was slight suprapubic tenderness, but no distention.

Urinalysis was as follows (catheter specimen): Clear amber, neutral in reaction, specific gravity 1010; albumin plus; sugar none. Microscopic: pus plus; red blood cells scattered; bacteria three plus (gram negative bacilli). 1 c.c. phenolsulphonephthalein given intramuscularly gave first hour excretion 45 per cent; second hour excretion 15 per cent; total excretion 60 per cent.

Blood counts were: Red blood cells 4,850,000 to 5,200,000 per cubic millimeter; white blood cells 4,850 to 8,000 per cubic millimeter; hemoglobin 70 per cent to 75 per cent. The Widal test was negative.

Urine cultures showed pure growths of Bacilli alkalescens.

Stool cultures showed 75 per cent of the organisms to be Bacilli alkalescens.

Blood cultures showed pure growths of Bacilli alkalescens.

Non-protein nitrogen of the blood was 45.4 milligrams per cent; creatinin, 1.32 milligrams per cent.

The diagnosis was now obvious: we were dealing with an acute bilateral pyelonephritis with septicemia caused by the Bacillus alkalescens. The patient was treated symptomatically and after four weeks of rather high remittent and intermittent temperature the fever disappeared.

On August 9 cystoscopic examination was made, using French No. 24 cystoscope which was easily introduced into the bladder. The bladder mucosa was inflamed. No tumor, ulceration or foreign body was seen. Both ureteral orifices were normal in size, shape and position. Both ureters were easily catheterized to the renal pelves and specimens obtained. The urines from both sides were practically the same and the culture from each urine showed a rich growth of Bacillus alkalescens.

It is interesting to note that the colonies from the left side were ten times as numerous as those of the right side.

The x-rays with catheters in position showed good kidney shadows,

somewhat low. There was no evidence of calculus anywhere in the genito-urinary tract.

Pyelography showed moderate dilatation of both pelves with some distention of the calices. Both kidneys were moderately ptosed. There was no evidence of ureteral dilatation.

The patient was discharged on August 17, 1932, as greatly improved. Her urinary and gastro-intestinal symptoms had completely disappeared. She still had, at times, some pain in the right costo-lumbar angle.

About one month later (September 13, 1932) she returned to the hospital for a check up. Except for a dull ache in the right loin, she felt very well. She had gained in weight and strength, and was able to do her usual duties.

Bacteriologic examinations were repeated. Her blood cultures were negative, stool cultures were negative, and cultures from both kidney urines were negative.

The patient was discharged on September 20, 1932. She has been under our observation off and on since, and has been apparently in good health.

DISCUSSION

This case to us is a most interesting one. Although the patient was primarily considered to have an acute infection of the kidney, yet the clinical picture simulated a blood infection. The marked gastro-intestinal symptoms, the malaise, the high fever, the enlarged spleen and the repeated low leukocyte counts all suggested typhoid fever. It was for these reasons that cultures of the blood, urine and feces were taken. When the cultures showed Bacillus alkalescens, then it was apparent that we were dealing with an acute pyelonephritis with septicemia caused by this organism. Cystoscopy with the bilateral ureteral catheterization corroborated this diagnosis.

The organism is apparently quite pathogenic for man as evidenced by the clinical picture of our patient. She appeared very sick and for about five weeks ran a fairly high fever. She lost a great deal of weight and strength and throughout its course the disease simulated typhoid fever very closely. As a matter of fact, the convalescence also resembled that disease.

SUMMARY

1. A case of Bacillus alkalescens pyelonephritis bilateral with septicemia and recovery is here reported.
2. Two similar cases found in the literature are reviewed.
3. A brief description of Bacillus alkalescens is given.

The bacteriologic studies were made possible through the co-operation of Professor Murray and his associates, of the Department of Bacteriology, Royal Victoria Hospital, Montreal.

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DISCUSSION

DR. JOHN R. CAULK (St. Louis, Mo.): I have been very much interested in Dr. Smith's paper particularly. In 1926, before this Association, I reported a hydrocalix resulting from a stricture of the infundibulum in which I was able to remove the stricture by sharp dissection through a nephrotomy incision. The functional result was excellent. I mean the pelvis was fine, the conformation good, function good, and symptoms relieved. The patient was free of symptoms for a long, long time. She is a very active social service nurse in our department. I hadn't seen her for about two years until the day I left, and for the first time in eight years she complained of a little grumbling in her right kidney region. Whether she has recontracted or not, I don't know, but I thought it might be interesting in my discussion to check this girl again and incorporate the findings in the discussion in order to determine the durability of resection of these strictures.

Dr. Lower, just previous to my report, had resected a kidney for stricture of the superior calix with a very satisfactory result.

The question of pregnancy, of course, is a very vital one to us. In 1917 I checked the kidneys in a long series of pregnant women and found large amounts of retention, particularly in the right, in 50 per cent of all normal pregnancies.

I was impressed, as were Drs. Crabtree and Prather, with the fact that almost invariably the obstructions seemed to be around the region of the superior strait. The late post-partum results have demonstrated almost invariably that strictures occur in this neighborhood.

I think, whether there is involvement of a single kidney or both kidneys, we are obligated to watch these patients very carefully. There has been a tendency on the part of the obstetricians not to use the ureter catheter as frequently as I feel, and as most of us feel, they should. I am a great believer in immediate catheter drainage, for the pyelitis of pregnancy.

I think we do not follow these people frequently enough. We should watch them very carefully on account of the fact that most of these obstructions which cause trouble come usually from the

fourth to the seventh month, and we have only a short period in which to supervise them, and we should do systematic catheterizations. Often after the relief of intrapelvic pressure, the kidneys empty themselves, and one will have very little trouble with most of them. Calisthenics, particularly the knee-chest position, will often help to get the uterus out of the pelvis and aid in the emptying ability of the kidney.

After the seventh month, we have had very little trouble except in the pretty severe infections, and it means that we must supervise pregnancies with the catheter and not allow so many of them to go on to interruptions.

I believe the catheter will save many interrupted pregnancies and certainly it possesses no danger. I have never seen a miscarriage attributable to manipulation.

DR. H. L. KRETSCHMER (Chicago, Ill.): I was very much interested in Dr. Crabtree's and Dr. Prather's paper. The thing that impressed all of us, I am sure, is the fact that so many women have nephrectomies who subsequently become pregnant and have no complications on account of the solitary kidney. In my experience as a consultant, it is rare, indeed, for me to come across a case where a lone kidney in a woman has caused any subsequent trouble during pregnancy.

In a recent study that we made at the Presbyterian Hospital, it was found that 96 per cent of all pregnant women who are normal, that is, have no infection or no urinary symptoms, show definite evidence of dilatation in the urinary tract. If we bear this fact in mind, namely, that upwards of 96 per cent of all pregnant women show the presence of dilatation, it is surprising that when a pregnant woman has only one kidney, the condition is not more frequently accompanied with infections and other serious trouble. All of Dr. Prather's pyelograms show evidences of dilatations in patients with only one kidney. We all know that dilatation is always present in every pregnant woman who has pyelitis.

Interesting, too, in our study, as in his study, was the fact that so many of these patients return to normal within two or three weeks, the dilatations having disappeared. In a very small group, however, the dilatations may persist as long as three months. In case the dilatation persists three weeks after delivery, the patient should be closely observed lest further complications should set in.

DR. WILLIAM F. BRAASCH (Rochester, Minn.): I am very much interested in Dr. Smith's paper on dilatation of a single calix. In the Clinical Proceedings of the Mayo Clinic, I reported a case some three years ago in which a similar condition was present in which Dr. Judd did a partial nephrectomy and with excellent results. There may be some difficulty in the differential diagnosis between a dilated calix and a cortical cyst which has ruptured into the calix. I have seen such a cyst, which was about 3 or 4 cm. in diameter, and which ruptured into a calix with subsequent infection requiring nephrectomy.

PRESIDENT FOWLER: Miss Hill, from the Brady Institute in Baltimore, is present, and I am sure the Association would be delighted to extend the courtesy of the floor to Miss Hill for a discussion of Dr. MacKenzie's very interesting paper.

MISS J. H. HILL (Baltimore, Md.): I won't intrude on this august society but a few minutes, but I was extremely interested in Dr. MacKenzie's paper, and it gave me the occasion to go over our blood cultures. I may say that for the last eight years we have done our blood cultures in our own departmental laboratory. Cultures have been taken whenever the temperature rose sufficiently to indicate it, and we were able to get cultures at the time of the rise of temperature, which I think has given us a much larger positive series than is obtained when the culture is perhaps taken the next day or whenever it is convenient. In that way, we have had in the past eight years 254 cases which showed definite blood stream invasion, and I was interested to find that thirty-eight of these, or, roughtly, 15 per cent, were due to B. proteus. That, I think, is much higher than I had any idea until I looked it up.

Fourteen of these cases were definitely transitory bacteremias which may be ignored here. That left us with twenty-one cases of very definite B. proteus septicemia in the blood. Five of these patients, after from three to four positive B. proteus cultures in each case, recovered. There were two cases of B. proteus septicemia in which the blood became sterile but the patient later died with genito-urinary infection, with B. proteus a major cause of death. There were, then, fourteen cases of fatal B. proteus septicemia; nine had definite pyelonephritis; seven were associated with postoperative wound infections with B. proteus, that is, of these thirty-five cases in which B. proteus was undoubtedly the etiologic

factor, there were fourteen bacterenias, twenty-one septicemias, with sixteen deaths, or 45.7 per cent of the total. So we feel that B. proteus in the genito-urinary tract is an extremely important organism which we must follow a good deal more closely than we have before. I may say all of these cases were associated with a B. proteus urologic infection.

When it gets into postoperative wounds, it is an extremely difficult problem which we haven't yet solved. I may say that we always make our cultures on blood agar plates by which that characteristic spreading growth of B. proteus may be observed. We also study it for its decomposition of urea in urea broth.

DR. GEORGE G. SMITH (Boston, Mass.): I am very much obliged to Dr. Caulk for calling to our attention the report of these two cases that had been seen by members of this Association.

I happened to be present when Dr. Lower operated on the patient he described here, so his report was very interesting to me. When the dilated calix is situated at one pole of the kidney, I have no doubt but that resection is the best thing to do. When it is situated in the middle of the kidney cortex, I think that draining the cavity and, if possible, destroying the lining will give relief from the condition. It is interesting to speculate on the etiology of this condition in these two cases that I reported. In these cases it seems unlikely that the condition could have resulted from the infection which was the cause of the present situation. In other words, it seems probable that there had been a certain anatomic condition of poor drainage of the calix which had existed long prior to the infection, the history of which was of very recent date.

DR. GEORGE C. PRATHER (Boston, Mass.): Since Dr. Kretschmer brought up the well-known point of dilatation in pregnancy, I think it has been an observation with us certainly that the women who have had a toxemia in pregnancy and who have had retrograde pyelograms or have been given intravenous pyelograms, have shown very little dilatation. If the recent work of Ansellmino and Hoffman on toxemias in pregnancy is supported by further study, their theory being that the toxemias are due primarily to changes in the pituitary gland, it will perhaps answer to some extent why we do not get dilatation and atony of the upper ureter and kidney pelvis as frequently in toxemia.

DR. DAVID W. MACKENZIE (Montreal, Canada): I should like to say a word on Dr. Crabtree's paper. In 1928, Dr. Duncan of the Obstetrical Department of the Royal Victoria Hospital, and Dr. Seng of our service took up a series of seventy-eight pregnant women, all free of symptoms of urinary disease.* In these there was found dilatation of the right ureter in 100 per cent of the cases studied. This dilatation began as early as the tenth week of pregnancy. Left ureteral dilatation was found in 69 per cent. A right-sided hydronephrosis was demonstrated in 87 per cent; a left in 50 per cent. Cultural growth of the kidney urines revealed a 9 per cent incidence of some form of coliform organism, and of those showing such growth, 5 per cent later developed clinical pyelitis.

Then Dr. Duncan took up our cases of women with one kidney. There were fifty-three women who had been nephrectomized. The pregnancies following nephrectomy ranged from one to five, with an average of two.

Two of these women in the series had tuberculosis of the solitary kidney. Three had chronic nephritis. The impression obtained was that pyelitis does not occur any more frequently in the nephrectomized woman than in the normal pregnant woman. When tuberculosis exists in the remaining kidney, these patients can carry through one pregnancy but further pregnancies are often unfavorable because of the likelihood of pulmonary extension.

There were no casualties of the fifty-three cases, perhaps because they were kept under more observation and more carefully handled than the ordinary.

To come back to our own paper here, it was very kind of Dr. Hill to come and to give us a report. As a matter of fact, what led us to put this small paper in the transactions was that though Proteus is an extremely common organism in the genito-urinary tract, it is nearly always associated with some trauma, instrumental or otherwise.

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RETROPERITONEAL PERIRENAL LYMPHANGIOMA*

HERMAN L. KRETSCHMER, M.D.
Urologist To The Presbyterian Hospital, Chicago
and
WILLIAM G. HIBBS, M.D. (by invitation)
Pathologist to The Children's Memorial Hospital, Chicago

The retroperitoneal tissues both above and below the kidney may be the seat of a variety of tumors, which may be either benign or malignant, cystic or solid. It is generally assumed that the benign tumors and cysts occur more frequently than do the malignant growths, and that the solid tumors are more commonly seen than the cystic.

Gobell (1901) was able to collect 101 cases of retroperitoneal tumors from the literature which he divided into the following groups.

Benign retroperitoneal growths	43 cases
Malignant retroperitoneal growths	32 cases
Either type of retroperitoneal growths	14 cases
Retroperitoneal cysts	12 cases
	101 cases

No case of retroperitoneal lymphangioma is to be found in his collection of cases.

Mauclaire (1910) studied the tumors of the retroperitoneal space and described about the same varieties as did Gobell.

Magoun (1919) reported a series of seventy-three cases of retroperitoneal tumors; fifty-three patients were operated upon, twenty-nine cases proving malignant, while eighteen were benign and the nature of six was not determined.

Having recently had the opportunity of studying a very rare type of retroperitoneal tumor we wish to report the following case.

Mrs. J. W., aged fifty-nine years, referred by Dr. R. C. Brown, was admitted to the Presbyterian Hospital, October 14, 1928.

The patient gave a history of an attack of nocturia and mild frequency about eight years before admission to the hospital.

For about eight years she has had an ache in the right upper quadrant of the abdomen. Various physicians told her she had an en-

larged right lobe of her liver. She never had jaundice nor an acute pain in the right upper quadrant. For several years, she had felt that there was a definite mass under the costal arch. When on her feet the mass felt heavy and dragged down somewhat. She had been told that she had liver trouble and had been placed on various dietetic managements.

For an indefinite period of time the patient had also felt a strain, or ache, or pulling in the right flank. Several weeks before admis-

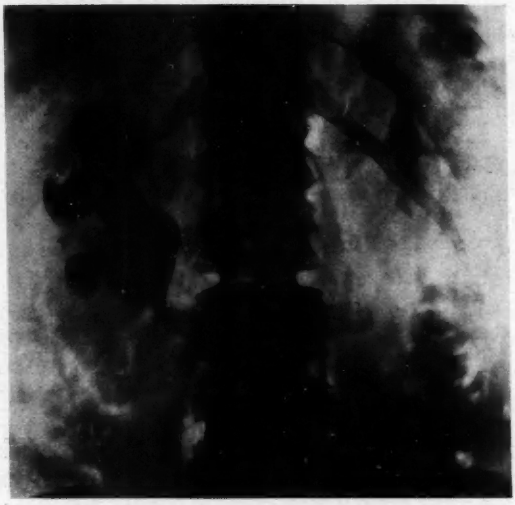

Fig. 1. Right pyelogram, showing a moderate hydronephrosis with marked dilatation and clubbing of calices. Left pyelogram, normal.

sion to the hospital she experienced a feeling of strain that ran down the right side and across the inguinal region to the groin and down the right leg on its medial side.

Urinary symptoms were absent. She has been troubled with constipation for some time.

Physical examination (Dr. R. C. Brown) showed the head, neck, heart and lungs, negative. In examining the abdomen a firm, smooth, globular mass was felt which almost filled the entire right upper quadrant. It projected down from under the costal arch, the lower border being on a level with the umbillicus, and extending almost to the midline. On deep palpation the mass moved down in such a way that it became readily palpable, bimanually. Some tenderness was present over the lower pole of the mass. Liver, spleen, and left kidney

were not palpable. Genitalia were normal and reflexes were normal.

Blood examination showed: Red blood cells, 3,130,000; leukocytes, 8,800; hemoglobin, 84 per cent.

Blood pressure was systolic 124; diastolic 80.

Roentgen-ray examination, October 15, 1928, was negative for stone and bone change.

Cholecystogram was negative.

Cystoscopic examination revealed a normal bladder. The left ureter

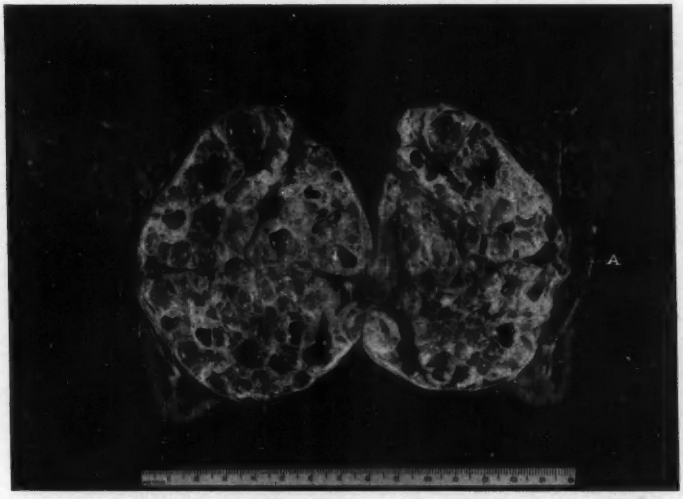

Fig. 2. Photograph showing the sharp line of demarcation between the kidney and the tumor. *A*—The dilated renal pelvis. Note cystic structure of the tumor.

catheterized without difficulty or obstruction. On the right side the catheter met an obstruction about 2 cm. from the orifice, which was overcome with some difficulty. Examination of the urine obtained at this time showed:

	Leukocytes per cu. mm.	Culture	Tubercle Bacilli
Bladder	310	Sterile	0
Left Kidney	0	Sterile	0
Right kidney	260	Sterile	0

Guinea-pig inoculation showed the bladder and right and left pigs negative for tuberculosis.

Right pyelogram showed moderate hydronephrosis with marked

dilatation and clubbing of the calices (Fig. 1). Left pyelogram showed a normal condition.

From the findings a diagnosis of tumor of the right kidney was made and operation advised.

Right nephrectomy was performed (H. L. K.) under ethylene-ether anesthesia, October 26, 1928. There was an uneventful convalescence and the patient was discharged from the hospital, November 16, 1928.

Description of Specimen (W. G. H.).—The gross specimen consisted of the upper and medial two-thirds of the right kidney to which

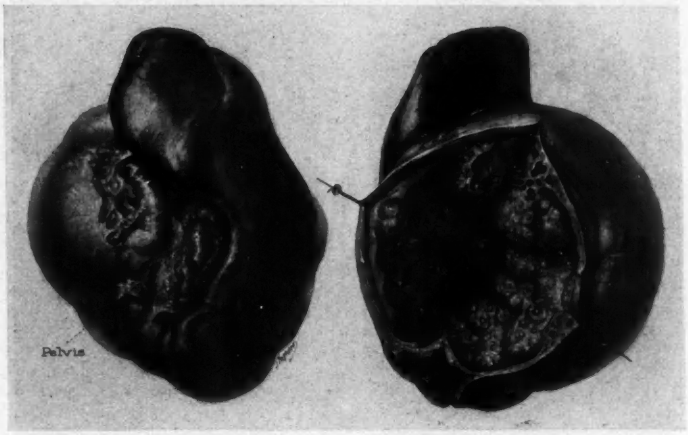

Fig. 3. Note thick capsule of the tumor which is made up of hundreds of separate cysts with firm thin gray walls.

was attached, laterally and to its lower pole, a firm semispherical, encapsulated mass which measured 8.5 by 11 by 9 cm. The complete specimen weighed 395 grams, and measured 14 by 10.5 by 10 cm. The tumor of the lower portion of this kidney was about four-fifths of the entire specimen.

On the surfaces made by sectioning, the kidney tissue was normal in color, the cortex was 6 to 8 mm. thick, had well-defined striations, and was clearly contrasted from the medullary portion. The kidney substance of the upper pole was 8 to 15 mm. thick. Here the capsule stripped easily and left a smooth surface.

From the upper pole, the kidney tissue thinned down on the outer surface to blend with the capsule of the tumor mass. *The kidney tissue was sharply defined from the tumor by a firm capsule 1 mm. thick* (Fig. 2). This tumor tissue within its capsule had *replaced*

the lower pole of the kidney and had compressed up and medial into the remaining portion of the kidney.

The tumor tissue, wherever it was cut (Fig. 3), consisted uniformly of hundreds of separate cysts with firm, thin, gray walls, which varied in size from 2 to 10 mm. in diameter. The cysts generally contained clear, pale brown fluid, but in isolated places, after formalin fixation, the content was a firm, clear gelatin-like substance which occasionally, in its centers, contained a homogeneous, opaque, yellow-brown material. In a few places, where the capsule was not adherent, the cysts

Fig. 4. Lymph cysts of variable size typical of the entire tumor.

occurred in clusters of eight to ten. They extended out from the main tumor mass, which was firmly compressed within the rigid capsule.

Cysts were not present anywhere within the kidney substance.

Microscopically the tumor mass consisted of simple cysts of many sizes. All of the cysts were lined with a single layer of flat, broad endothelium and contained lymph (Fig. 4). Only in isolated places were the endothelial cells more than one cell layer thick. These places were at the site of a clump of smaller cysts, evidently at a place of compression by adjacent cysts. Here the compressed cyst was scant in lymph, and the hyperplastic endothelium was in the recesses of the cyst and consisted of stratified cuboid endothelium proliferating centrally into the cyst from the cells of the peripheral lining.

Where the cysts were larger their walls were thin so that the space between the lining endothelium of adjacent cysts was a delicate band of fibrous reticular tissue. Elsewhere, however, the endothelial linings of adjacent cysts were separated by dense fibrous reticular tissue which was sparse in blood-vessels. In places, this fibrous reticulum might occupy all of a low-power field, and its central portion was sparse in nuclei with compression atrophy, hyaline degeneration, and isolated deposition of calcium.

The entire tumor mass, which consisted of lymphatic spaces, was

Fig. 5. Fibrous cyst-wall containing solitary cysts with compression of the kidney. Lymphocytic infiltration.

separated from the kidney substance proper by a dense fibrous tissue capsule (Fig. 5). Occasionally this capsule retained isolated kidney tubules which were in various stages of atrophy.

In the kidney where the tumor had compressed it, there was a rather dense infiltration of lymphocytes. The kidney substance adjacent to the tumor capsule was atrophic, the tubules stained poorly and many glomeruli were hyalinized. This change of kidney tissue was only in that part which was adjacent to the tumor. The kidney tissue proper was free of histologic evidence of disease. Cysts were not present anywhere within the kidney substance.

REVIEW OF THE LITERATURE

The literature on the subject of retroperitoneal lymphangioma is extremely scanty. In the reviews of retroperitoneal tumors by Gobell (1901), Mauclaire (1910), Magoun (1919), Andrews (1923), and Schmidt (1923), no mention is made of this type of neoplasm.

Lecene (1919), in his careful review of the past literature relative to pararenal tumors, includes one lymphangio-sarcoma (Lund, 1901) in his collected series of 113 cases.

Gaudier and Gorse (1913) reported a retroperitoneal cystic lymphangioma, and drew attention to the fact that a diligent search of the literature revealed no strictly analogous case. They reviewed, however, the cases of retroperitoneal lymph cysts reported by Kilian (1886), Narath (1886), Winter (1895), and Penkert (1902), due to the fact that these lymph cysts showed some points of similarity to their own case.

Westman (1925) reported a retroperitoneal lymphangioma, which was retrocecal in position. He mentions no similar case in the literature.

Burhaneddin (1931) reported a multilocular cystic retroperitoneal lymphangioma, his comment being that he has not succeeded in finding a similar case in the literature.

McFadden (1931) reported the successful operative removal of multilocular cystic retroperitoneal lymphangioma.

While there are a number of cases reported of chylous and lymphatic cysts, the four cases mentioned above constitute the only cases of true retroperitoneal lymphangioma of which we are able to find a record. These, with the addition of the tumor herein reported, furnish five such cases for study.

Our survey would lead us to concur with the opinion of McFadden who feels that many of the retroperitoneal cysts described in the literature were probably true lymphangioma and not cysts arising from local peritoneal cells derived from the urogenital ridge, as described. We include in our study, however, only those cases which were proved by microscopic study to be true neoplasms of the type of lymphangioma.

Kaufman emphasizes the necessity of differentiating between lymphangioma, a new growth, and lymphangectasis, a simple dilatation of the lymphatics.

RETROPERITONEAL PERIRENAL LYMPHANGIOMA

Author	Age	Sex	Duration Symptoms	Symptoms	Clinical Diagnosis	Method of true Diagnosis	Location of Tumor	Size	Treatment	Outcome	Remarks
Gaudier and Gorse (1913)	4 yrs.	M	..	Inguino-scrotal tumor (fluctuant), pressure on which transmitted to right lateral abdominal wall	Cystic Abdomino-scrotal tumor	Operation and Examination of Specimen	Right Retroperitoneal region from lower pole of kidney to pelvis with extension into inguinal region	25 cm. x 10 cm. x 12 cm.	Surgical extirpation	Good	This tumor showed a finger-like extension into scrotum
Westman (1925)	58 yrs.	M	About 24 hours	Tenderness over right side of abdomen, pain right side of abdomen, nausea and vomiting	Acute appendicitis	Operation and Autopsy	Retrocecal, surrounding cecum and appendix	Size of fist	Exploratory Operation	Death from gangrenous appendix and appendiceal abscess	This tumor prevented operative removal of gangrenous appendix and this caused death
McFadden (1931)	5 yrs.	M	4 yrs. 4 days	Enlarged abdomen, Acute abdominal pain and distention with bulging umbilicus	Inflamed appendix or inflamed gland of tuberculous peritonitis	Operation and Examination of Specimen	Retroperitoneal extending from lower pole of right kidney to inferior surface of the liver		1. Drainage of cyst 2. Extirpation of tumor 15 months later	Good	
Burhaneddin (1931)	40 yrs.	M	3 yrs.	Tumor size of fist above right inguinal fold which enlarged to reach right costal arch	Inoperable Sarcoma	Operation and Histological Study of Specimen	Right retroperitoneal region, bulging into abdomen and displacing cecum and appendix	Weight 6.4 kg. 45 cm. x 35 cm.	Excision by abdominal route (pararectus incision)	Good	
Kretschmer (1933)	59 yrs.	F	8 yrs. Several yrs.	Pain right upper quadrant of abdomen. Mass which almost fills entire right upper quadrant of abdomen	Tumor of right kidney	Operation and Histologic al study of specimen	Attached to lower pole of the kidney	8.5 cm. x 11 cm. x 9 cm.	Nephrectomy	Recovery	

ETIOLOGY

In a consideration of the etiology of retroperitoneal lymphangioma we must distinguish carefully between retroperitoneal and mesenteric cysts and true lymphangioma.

According to Ewing, retroperitoneal lymphangioma occurs in children and adults as a multilocular cavernous and cystic tumor, originating along the spinal column, and ramifying into the pelvis behind the kidney or colon, upward to the liver, spleen and into the omentum. He states that "the very early stages and exact origin of these tumors have not been demonstrated," and adds that their neoplastic nature seems assured "since the walls contain cellular connective tissue, often much muscle and lymph-follicles."

The origin of retroperitoneal tumors "is at the best a matter of speculation. All types of tissue are in the retroperitoneal space and may at any moment undergo abnormal growth," is the opinion voiced by Magoun.

Burhaneddin mentions the various types of retroperitoneal cysts, and the theories of their etiology, but concludes that his own case was a cystic lymphangioma, a true neoplasia.

The various angiomas, says Harris, must have their origin in a developmental anomaly in structure of certain vascular segments which do not fit into the circulatory system, and which retain embryonal characteristics. The congenital origin of the majority of these tumors speaks strongly in favor of a tissue predisposition as a prominent factor in their genesis.

McFadden says that, while its anatomic relation might have suggested the origin of his case of retroperitoneal tumor (cystic lymphangioma) from the urogenital ridge, examination revealed it to be a true lymphangioma.

The old literature contained references to lymph cysts, says Westerman, and the opinion at that time seemed to regard such tumors as a result of lymph stasis, but at present they are regarded as true new growths.

Brandsburg says that the majority of lymphangiomata occur in childhood, and finds that they occur with equal frequency in the two sexes. There are many theories as to their etiology and he enumerates the following:

1. The retention theory which explains lymphangioma on the grounds of mechanical pressure.

2. The theory of a disturbance of secretory function of the endothelium of the vessels, causing hyperproliferation of lymph, or disturbance of permeability of the endothelium.
3. The inflammatory theory.
4. The embryonal theory.

Brandsburg feels from his studies that the embryonal theory is the most acceptable. It explains the lymphangioma on the grounds of a defect in the embryonal organization of the lymphatic system, small segments of tissue retaining their embryonal characteristics.

PATHOLOGY

A lymphangioma is a tumor composed of lymph vessels. It is an organoid structure consisting of endothelial cells and supporting connective tissue, both being involved in the neoplastic process.

Ewing states that the clinical conditions which fall in the general class of lymphangioma "include a variety of slowly growing congenital single or multiple tumors of the skin, subcutaneous tissues, deep areolar structures and muscles of neck, trunk, lip, tongue, eye and orbit." In the pathogenesis of these conditions many factors are concerned, says Ewing, hence it is more difficult to distinguish between lymphangioma and lymphangectasis than between true and spurious hemangioma.

According to Ewing the simple occlusion of lymph channels may be followed by extensive varicosities resembling lymphangioma. He notes that the general clinical features apparently offer an important means of recognition of lymphangioma, but even so, there are a large number of investigators who include in the class only such processes as show a congenital origin and a progressive course, with absence of traumatic and inflammatory factors.

Kaufmann states that on section a lymphangioma shows dilated spaces lined with endothelium, which are filled with clear or slightly cloudy lymph. The walls are fibrous and often quite muscular. The interstitial tissues contain fat and foci of lymphoid structures, and after section of the tumor the cavities collapse. This did not occur in our case.

Kaufmann further states that where connective tissue overgrowth is greater between the spaces, the tumor is firmer and may be termed lymphangio-fibroma. He affirms that in the individual case it is sometimes difficult to state whether the mass is a true neoplasm of lymphatic vessels or only a dilatation with secondary

thickening of preformed vessels with some muscular hypertrophy. A sharp differentiation should be made between lymphangectasis (simple dilatation of lymph vessels) and the lymphangioma, a new growth.

Sick (quoted by Kaufmann) believes that the starting point of many lymphangiomata is in an isolated vessel or in primitive connective-tissue-rest which proliferates into new lymph vessels.

In Burhaneddin's case (retroperitoneal cystic lymphangioma) the tumor was of a greenish white color, thin walled and made up of cysts of various sizes filled with clear fluid. The tumor had no connection with tissues around the kidney.

Upon microscopic examination the inner walls of the cysts of Burhanedin's tumor were seen to be lined with oblong, partly flat endothelial cells. On the external surface and in the interstices between the cysts was seen developing angiomatous tissue. In isolated places the interstitial tissues showed flat large cell elements which seemed to fill the spaces of these tissues. The diagnosis from a study of the structure of these walls was cystic lymphangioma.

McFadden's case appeared at first sight at operation as a large horse-shoe shaped cyst which filled the lower abdomen. In the midline it reached about an inch above the bifurcation of the aorta, and in the flanks it extended to both kidney pouches. It extended into the pelvis behind the mesosigmoid and mesorectum, was closely adherent to the perinephric fat, and tense and multilocular. In one area colonies of small cysts on the wall of the cyst gave the appearance of frog's spawn. The cysts contained turbid fluid in which were scattered flakes of lymph. Microscopic study showed this tumor to be a true lymphangioma, with a matrix mostly of fatty tissue, though in places it was fibrous with strands of plain muscle, among collagen fibrils. In the matrix was a sort of spongy network of channels, some long and narrow, some in the form of wide spaces. The lining of these was a single layer of flattened endothelial cells, absent in some places, which were supported by fibrous tissues.

Collections of lymphocytes were seen, sometimes in the walls of the spaces, sometimes lying irregularly in the meshes of the matrix, sometimes in spaces by themselves. Scattered foci of polymorphonuclear leukocytes gave evidence of superadded inflammatory reac-

tion. The author notes the similarity of appearance of the cavernous lymphangioma to the congenital hygroma of the neck or axilla.

In Westman's case the tumor surrounded the cecum on the anterior, external and posterior sides. It was of the size of a clenched fist, and composed of small cysts. This growth was fixed against the posterior abdominal wall, but was easily loosened from the lower pole of the right kidney. It had no union with the appendix, intestines, or other organs, and was diagnosed after microscopic study as a lymphangioma cavernosa. There was neither dilatation of lymph vessels nor any evidence of lymph stasis.

Gaudier and Gorse remark that the pathology of the retroperitoneal lymphangioma is obscure. They note that Penkert discusses the various hypotheses as degeneration of ganglia, dilatation of lymphatics and cystic degeneration of a cavernous lymphangioma. Other authors are inclined to think that the condition is a congenital malformation. Gaudier and Gores are of the opinion that the true explanation is wanting.

The tumor in our case, by its growth, caused pressure atrophy of the lower pole of the kidney and was attached to the kidney.

SYMPTOMS AND CLINICAL FEATURES

Retroperitoneal lymphangiomas present no clinical features which would serve to distinguish them from other retroperitoneal growths.

Retroperitoneal tumors are, as a rule, "silent" until their size is such that pressure symptoms arise.

Burhaneddin noted that difficult respiration and ureteral pressure are two usual effects of such tumors. In his case (cystic lymphangioma) the neoplasm caused symptoms of ureteral obstruction which were relieved after the operative removal of the mass.

In McFadden's case (retroperitoneal lymphangioma) the patient, who had had an enlarged abdomen for four years, suddenly developed acute abdominal pain and distention of such a degree that there was protrusion of the umbilicus. Palpation revealed no tumor and rectal examination was negative. A clinical diagnosis of acute appendicitis or inflamed glands of a tuberculous peritonitis was made.

Westman's case (retroperitoneal lymphangioma) had apparently caused no symptoms and was discovered incidentally at operation

for acute appendicitis. The size and position (retrocecal) of the tumor prevented the removal of the gangrenous appendix, thus, causing the death of the patient in an indirect manner.

A prolongation of the tumor, in the case of retroperitoneal lymphangioma recorded by Gaudier and Gorse caused an inguino-scrotal tumefaction, which served to direct attention to the growth. On examination it was noted that the pressure on the scrotum was transmitted to the right lateral abdominal wall, at which point a large rounded, painless tumor was palpated. The clinical diagnosis was abdomino-scrotal tumor of unknown nature.

In his study of the retroperitoneal tumors seen at the Mayo Clinic, Magoun found the following as the most prominent symptoms of the group of benign neoplasms:

Abdominal mass	15
Loss of weight and strength	10
Abdominal pain	5
Increase in size of abdomen	2
Pain in back	2
Bloating	1
Constipation	1
Fullness and belching	1
Paresthesia in right leg by pressing on growth	1

Magoun noted that these symptoms accompanied the group of malignant retroperitoneal tumors, hence, he concluded, that clinically, it was highly improbable that one could distinguish between the nature of the tumors.

DIAGNOSIS

The chief diagnostic aids in the diagnosis of retroperitoneal tumors are cystoscopy, ureteral catheterization and pyelography, since the differential diagnosis of retroperitoneal growths must include a consideration of kidney tumor, hypernephroma, hydronephrosis and pyonephrosis, and perinephritic abscess. Furthermore, consideration must be given to enlargements of the spleen, both solid and cystic tumors of the pancreas, as well as in rare instances to tuberculosis of the lymph nodes.

One of the older but simple aids in the diagnosis, namely, inflation of the colon with air, has been almost practically displaced with the roentgen ray.

When the retroperitoneal tumor occurs low in the abdomen it may be confused with lesions of the uterus or ovaries. Because

of the painless nature of the enlargement, retroperitoneal tumors have led to an erroneous diagnosis of pregnancy.

Of importance to remember is that a diagnosis of the nature of the growth, as to whether it is benign or malignant, as well as the differentiation of lymphangioma from other retroperitoneal growths, can be established only upon the histologic examination of the tumor, since both are extremely difficult unless histology is utilized to clarify matters.

TREATMENT

At operation for retroperitoneal tumors it is not infrequently necessary to do a nephrectomy, as in our case, the kidney being engulfed by the tumor, and removal of the latter without the former being a mechanical impossibility. In other instances the kidney has atrophied as a result of the pressure of the neoplasm and is not worth saving, hence the importance of a thorough pre-operative study of the function of both kidneys preliminary to operation for retroperitoneal tumor. Not only is this important from a diagnostic viewpoint, but this knowledge may be essential during operation, when, as has been stated, nephrectomy may be necessary in the removal of the tumor.

Hofstatter and Schnitzler note that where tissue bands exist between kidney and tumor, it is frequently impossible to tell macroscopically during the operation whether they are simple adhesions or extensions of the growth. Such a condition would predispose the surgeon to do a nephrectomy, providing he knew that the function of the opposite kidney was satisfactory.

Hartmann and Lecene removed the kidney in eighteen out of twenty-seven cases of pararenal tumors on which they operated.

The chief operative difficulty in the removal of retroperitoneal growths lies in the dissection of the tumor adhesions to the mesentery and intestines (Westman, Lecene, Bettman and Serby). These authors note that in such dissection the injury to mesenteric vessels may be unavoidable, and may necessitate resection of portions of the gut. They urge that at operation for retroperitoneal tumors the surgeon and operating instruments should be prepared for such an emergency.

It is generally conceded that the ideal treatment of benign retroperitoneal tumors, including the rare cystic lymphangioma, is surgical extirpation. On the other hand, Burhaneddin writes that it

is surprising that the extirpation of such large cystic tumors is frequently possible. Ours was easily done.

Westman states that, although complete extirpation is the ideal treatment for cystic lymphangioma of the retroperitoneal regions, drainage, with tamponade and the suture of the cyst edges to the peritoneum, may be done when the tumor is unilocular and when its size and attachments make complete extirpation impossible. He also states that radium may be used when, for any reason, the tumor is inextirpable.

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NEPHROSTOMY

REPORT OF CASES

GEORGE R. LIVERMORE, M.D.

Memphis, Tennessee

The benefit that may be derived from nephrostomy does not seem to be appreciated by the profession. Although Cabot and Holland, Boyd and others have reported how satisfactorily it has served them, it is not being used as frequently as its worth demands. It has been such a boon to the author on numerous occasions, it is with a sense of appreciation of its value that he brings his experience to you.

Some years ago I performed nephrostomy in an operation devised to induce diuresis in the anuria of bichloride of mercury poisoning. This consisted of a rapid decapsulation and a nephrostomy, the incision being made parallel and just posterior to the convex border of the kidney, and gauze saturated with 10 per cent ichthyol in glycerine packed through the nephrotomy wound into the kidney pelvis. Although in the two cases in which it was used, both patients died, it proved its worth in establishing the excretion of urine, which continued up to the time of death. This was before the discovery of sodium thiosulphate and before we knew so much about the corroding effect upon the entire gastro-intestinal tract.

While in New York in the fall of 1931, Dr. W. H. McNeill, Jr., let me see a case of anuria due to bichloride of mercury poisoning on his service at Bellevue Hospital. The patient was a young married woman who had swallowed five bichloride of mercury tablets of 7.5 grains each, three days before I saw her. She had voided a few ounces of urine the first twenty-four hours and none since. Sodium thiosulphate, gastric and colonic irrigations, and intravenous and subcutaneous fluids had been given without effect. I suggested to Dr. McNeill to try the method which I had used, and with the patient's consent he did so. I am glad to report that diuresis began immediately following the operation and the patient recovered.

The other indications for nephrostomy, as given by Cabot and Holland, are the presence of obstruction which cannot be satisfactorily remedied by some other method: (1) acute obstruction either of both ureters, or of the remaining ureter, as in calculus anuria or malignant disease obstructing the ureter, (2) hydronephrosis or infected hydronephrosis, in which the cause of obstruction may be removable, but in which drainage of the kidney as a temporary measure is indicated to improve function, (3) renal calculi with badly damaged kidneys, (4) carcinoma of bladder occasionally in cases thought suitable for cystectomy, (5) failure of the musculature of pelvis, ureters and bladder to evacuate urine, (6) renal infection without high grade obstruction to avoid renal infection and allow renal recovery.

The indications in the cases I herewith report were as follows:

1. Anuria from acute nephritis of mercurial poisoning—three cases already mentioned.

2. Anuria due to stricture of the ureter—one case.

3. Failing kidney function from obstruction of the ureter due to ureteral calculi—two cases.

4. Infected hydronephrosis in the one functioning kidney due to kinking of ureter—one case.

The technic employed (except in the bichloride of mercury poisoning cases, which has already been mentioned) is as follows: The kidney is exposed, and freed, if possible. (In several of my cases that could not be done.) The method of Cabot of opening the pelvis and passing a U-curved sound into this opening, and out through the cortex at a point that satisfactorily drains the lower calix, is excellent, but in that type where the kidney cannot be freed, an opening may be made in the convex border, or the posterior surface of the kidney and the pelvis entered.

I have not used the winged catheter, advocated by Cabot, but relied upon a No. 22 to 35-F catheter, cutting off its tip so as to have an opening in the end. The method employed to retain it in the pelvis is by suture to the capsule of the kidney with No. 2 plain catgut sutures, and it is also anchored to the skin by two of silkworm gut. When the sinus has been well formed, a new tube may be easily inserted and held in place by adhesive strips through a safety pin in the tube. All of these patients have uremic symptoms and most of them are very anemic. Therefore, all measures

for the promotion of diuresis must be instituted. Transfusion of whole blood not only improves the patient's general condition, but also increases kidney function.

CASE REPORTS

Case 1.—Mrs. C. D. O.. white, married, aged 24, had a history of pain, frequency and burning with fever and pain in upper right quadrant and back. She had cystitis when a child. For the past eight years she had had pain at intervals in the right loin and back, and attacks of nausea and vomiting. She had been treated for gall-bladder infection for the past four years, and did improve under duodenal drainage, but pain in the right loin and urinary symptoms persisted.

I made a cystoscopic examination and made pyelograms on September 5, 1926. A large right hydronephrosis and a stricture of the left ureter were found. P.S.P. output from the right kidney was 0, from the left 17 per cent. Right nephrectomy was done September 8, 1926. The patient left the hospital September 19, 1926, in splendid condition with instructions to return for dilations of the stricture of her left ureter. She was not seen until March 17, 1927, when she entered the hospital with a history of anuria for the past forty-eight hours. Cystoscopy was performed at 10 A. M., and a No. 6 catheter met obstruction 6 cm., up the left ureter, then passed to the pelvis of the left kidney.

There was no urine in the bladder and none flowed from the catheter in the pelvis. Blood chemistry showed N.P.N., 128 mg., and creatinin 5.7 mg., per 100 c.c. of blood. At 7:30 P. M., as there had been no drainage from the catheter since its introduction, despite the fact that all measures for the promotion of diuresis had been carried out, the patient was taken to the operating room and a decapsulation and nephrostomy performed. In the kidney pelvis 150 c.c. of bloody-stained urine were found. A No. 18-F catheter was sutured in the pelvis and urine was draining from it when the patient returned to her room. It increased in amount until 2 A. M., when it was quite free, and all dressings were saturated. She continued to improve and five days after operation her N.P.N. was 66, and creatinin, 2.25; two days later N.P.N. was 56, and creatinin, 1.86. Four weeks after nephrostomy her N.P.N. was 28 and creatinin, 1.85. Cystoscopy was done on April 2, 1927, and the stricture dilated to a No. 12-F. She had violent reactions following cystoscopy, so she said she would rather wear the nephrostomy tube than to submit to cystoscopy. This she has done ever since, having it changed about every three months. When last heard from, two months ago, she was in good health and still wearing the tube.

Case 2.—Mrs. D. K., white, widow, aged fifty-two, gave a history of operation for stone in the right kidney September, 1921, and stone the size of hen's egg removed from the pelvis. The ureter was detached

from the pelvis, but was sutured back. On November 28, 1921, a stone the size of a walnut was removed from the left kidney pelvis. The wound on the left side healed in a few months, but there was a urinary fistula on the right which continued to drain until July, 1931, when it closed.

Cystoscopy was performed at this time by another urologist who told her the left kidney was "dead." She had lost 20 pounds in weight, and had gradually lost strength since the sinus closed. For the past two months the right kidney had been quite painful, and had increased in size until it was as large as a cocoanut. The patient had recently suffered from nausea, vomiting, dizziness, headaches and extreme weakness, and there had been a throbbing pain and a feeling of tension in the right kidney.

I saw her first on February 22, 1933. The right kidney was palpable as a large tense painful mass, the size of a cocoanut, and the lower pole was almost on a level with the umbilicus. P.S.P. bladder specimen first hour was 0; second hour, mere trace. N.P.N. was 83.3 mg.; creatinin, 3.5; hemoglobin, 45 per cent; red blood cells, 2,473,000; leukocytes, 6,400. Right nephrostomy was performed February 23, 1933. The right kidney was a greatly distended hydronephrotic sac. The kidney cortex was less than one-half inch thick on the convex border, though there was slightly more kidney tissue in the lower pole. When the nephrotomy incision was made, 2,000 c.c. of purulent urine spurted out as though under great pressure. A No. 35-F catheter was sutured in the pelvis. The tube was draining urine when the patient left the operating room, and it drained 600 c.c. in nine and one-half hours, besides saturating the dressings. The patient had marked uremic symptoms for about a week, then cleared up following a transfusion, and made a nice recovery. She is wearing the tube and is gaining in strength. The P.S.P. although still poor, is much improved.

Case 3.—A. C., white, male, married, aged fifty-eight, has had chronic pyelonephritis for twenty-five years, and has had cystoscopy performed on an average of once a month during this entire time. In the past five years two calculi had formed in each kidney pelvis. There was also one in the lower pole of the left kidney. The kidney function remained remarkably good until the calculi developed, when, with repeated ulceration, sloughing and profuse hematuria, the function of both had been much impaired. Six months previously a calculus was found in the left ureter one-half way to the bladder. A catheter was easily passed by the calculus to the left pelvis, and 15 c.c. of very purulent urine withdrawn. P.S.P., right, was 5 per cent; left, 5 per cent. Two months previously he had left ureteral colic, rigors, high fever and sweats.

A catheter passed to the left kidney pelvis relieved him for two weeks, but on removal of the catheter his symptoms returned. An

attempt was made to replace it, but it would not pass beyond the stone. With both kidneys so badly damaged, I felt a nephrostomy offered the best chance. This was done. A perirenal abscess was found and a large amount of foul colon pus was evacuated. The left kidney was densely adherent and in the presence of so much infection it was deemed best not to free it. Therefore, an incision was made in the posterior surface of the kidney, and the pelvis was entered. About 180 c.c. of foul pus were evacuated. A No. 22-F catheter was then sutured in the pelvis, and the pelvis was irrigated with saline and then with 2 per cent mercurochrome. Except for rather marked uremic symptoms for about a week, the patient made a nice recovery. Two months later I removed the stone from the left ureter, and allowed the nephrostomy wound to heal. The patient is now enjoying remarkably good health.

Case 4.—G. S., white, male, married, aged fifty-six, had a right nephrectomy for nephrolithiasis and hypernephroma, December 5, 1932, and later complained of aching pain in the left loin with occasional attacks of left renal colic. Two small stones were found in the left kidney cortex, and one about 2 cm. wide, one-half way down the left ureter. At operation two stones were removed from the cortex by nephrotomy. Much time was consumed in freeing the kidney and locating the stones, also, in x-raying the exposed kidney to be sure all fragments of stones were removed. An attempt was made to locate the stone in the left ureter, but as the patient's condition became very grave, I thought it best to do a nephrostomy and remove the ureteral stone later. This was done, and a No. 20-F catheter was sutured in the pelvis. Except for mild uremic symptoms, the patient made a nice recovery, and left the hospital on the twenty-fourth day, having been given one transfusion on the sixth day. He is improving, and will return later for cystoscopic attempts to remove the stone in the left ureter, and if this fails, I will operate.

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DISCUSSION

DR. ROGER C. GRAVES (Boston, Mass.): I should like to propose another indication for nephrostomy which Dr. Livermore did not include in his list and which I believe to be important. I refer to the extreme case of pyelitis in pregnancy, a condition which is of particular interest this morning in view of our earlier discussions. I have encountered two such patients within the past year. The first case is about to be published, the report being made by myself and Dr. Phaneuf of Boston who was the obstetrician in charge. The second patient I have seen more recently, and as her case is practically identical with that of the first one, I will relate it briefly.

She was a young woman in the twenties—I am describing this entirely from memory—about five and a half months pregnant, in her first pregnancy. She developed what at first seemed to be an ordinary pyelitis of pregnancy, but she went on to more extreme degrees of toxemia than we ordinarily encounter.

Cystoscopic investigation found a marked retention in the right kidney of urine which was heavily infected with colon bacilli and staphylococci. We carried out all the usual measures, both medically and urologically. I washed the right renal pelvis carefully, on two separate occasions, and instilled mercurochrome. I did everything that I felt it was safe to do in the presence of so active an infection; it did not seem safe in this case to leave an indwelling catheter within the ureter, for fear of causing an abscess or more complete obstruction. The patient was very sick and extremely toxic. There was no significant response to the cystoscopic treatments, and it was quite apparent that we were headed for disaster unless something more could be done.

Finally, because of the very satisfactory experience with the first case a short time before, I advised nephrostomy. This was done entirely under novocain as it seemed unsafe in this patient's very critical condition to consider any other form of anesthesia. She was greatly reduced in weight. She was unable to take any nourishment because of constant vomiting. She was approaching a jaundice from toxemia. The pulse was rapid and these unfavor-

able signs persisted in spite of anything that we had been able to do. The nephrostomy was very simple and comfortable under novocain, and the improvement was practically immediate. The patient began to take nourishment. Her fever subsided. She improved enough to be able to go home with her nephrostomy tube in position. She was up and about for the remaining time of her pregnancy, and finally came back into the hospital in normal labor within three weeks of term. There was a low forceps delivery and much to my satisfaction, as in the first case, the nephrostomy sinus was closed and completely dry within a few hours after the birth of the child.

To any who may feel that an interruption of the pregnancy might have been a simpler way out for this patient, I can say only that this might have resulted in the saving of the mother, whereas the nephrostomy which succeeded so well in the case of these two patients, not only saved the mother, but resulted also in the successful delivery of a normal baby.

DR. ALEXANDER RANDALL (Philadelphia, Pa.): I might add a case for Dr. Kretschmer's inclusion, although at the present time it will have to go down as an angioma without any specific positiveness in regard to the ultimate diagnosis. Unfortunately, this boy, the third son of a family of four, was run over about five years ago by a wagon, which led to a prolonged convalescence from an injury to his right leg, with osteomyelitis as a complication.

Three years ago, while wrestling with one of his older brothers, he suffered what might be termed an acute abdominal catastrophe, severe shock and pain, with marked abdominal rigidity. He was rushed to the hospital, and under the care of a general surgeon, the obvious thing was done; his appendix was removed. His appendix being found normal, abdominal exploration revealed that apparently there was a left-sided mass. Hematuria had been present.

The surgeon made a second incision into the peritoneum on the left side, and thereby proved that this mass undoubtedly was a retroperitoneal hematoma, so he closed the incision. A long, protracted convalescence began, with a gradual subsidence of the mass, symptoms, and so on. The growth of the patient has been retarded but his mentality is especially acute.

Last fall he again got into difficulty following his normal childhood physical activity, for while wrestling or playing at school,

he suffered a second attack of acute abdominal left-sided pain, and when I saw him later at the hospital, hematuria was present and there was a mass filling the greater part of the left abdomen and definitely going downward and reaching into the bony pelvis.

Rest and quiet improved his condition to a degree except that there was marked anemia, a mild leukocytosis, a low-grade fever, and with it very marked obstipation and great frequency of urination, the hematuria practically disappearing.

Feeling that something had to be done to relieve pressure if nothing else, I was foolish enough to attempt an exposure of the mass, hoping perchance to find something infectious. Going through retroperitoneally just inside the left anterior superior spine, I came down upon the capsule of the mass. Again, foolishly, I went boldly through this to find myself encountering a very vascular growth. I removed a portion of it, enough for biopsy, plugged the hole with all the iodoform gauze that seemed necessary, and promptly backed out. It was unquestionably a neoplasm, unquestionably an angioma, and I was of course fearful of persistent bleeding.

The boy again came through rather remarkably well. Drains were gotten out after a long interval on purpose, one or two transfusions were given, and when ready we started him on deep x-ray therapy. The response has been interesting. The tumor on study was composed of an undoubtedly embryonic form of cell and undoubtedly an angioma. It has been termed a hemangioma rather than a lymphangioma.

This mass, filling the whole left side and extending past the midline suprapubically, disappeared under x-ray therapy and when at its best at the end of last June, one could make out possibly something that seemed the size of a hen's egg situated in the left hypogastrium. There were no longer any subjective symptoms.

The boy was kept very quiet during the last summer and during the fall. He was always anemic, not growing very much but gradually going ahead, with poor appetite, though given tonics, and so on.

He entered school last fall in probably his best shape in years and it began to be difficult again to hold him down. It was only a month ago when the master of the school called his mother on the telephone to tell her that the boy had had another catastrophe.

Again a boy had fallen on him in a "rough-house" and when his mother arrived at school, he was doubled up like a jack-knife and in excruciating pain. It was just a question of whether or not he could stand the trip home in the limousine, but she got him there, and when I saw him he was beginning to relax and his condition improved. Again vesical symptoms stood out and again there was board-like rigidity.

Under purely supportive treatment, conditions have improved so much that he is back at school. There is again palpable an increased mass. It probably is an intratumor hemorrhage. He is again free of subjective symptoms of any great moment.

We are at the cross-roads. He has had his full saturation of x-ray. It will probably take very little more of it to keep him to 100 per cent saturation.

I think ultimately we will be able to add the whole story to your group of cases, Dr. Kretschmer, but it is a very, very difficult problem to handle, and this one has been doubly distressing to me occurring as it has in a child of one of my intimate friends.

Dr. George R. Livermore (Memphis, Tenn.): I am glad Dr. Graves brought up the use of nephrostomy in pregnancy. I have never tried it in such cases. As a rule, as Dr. Caulk suggested, we have been able to relieve with the ureteral catheter and when unable to do so, pregnancy has been interrupted. If nephrostomy is a method by which this could be obviated, it certainly is well worth while.

Dr. Keyes' suggestion of its use in tuberculosis seems to me an excellent thing. When you get these intractable bladders, after one kidney has been removed and the person is so perfectly miserable, it seems to me that something of that type rather than putting the ureters into the bowel is simpler and less dangerous to the patient.

A CONSIDERATION OF THE DEVELOPMENT OF POLYCYSTIC KIDNEY

CHARLES MORGAN McKENNA, M.D., and (by invitation) OTTO F. KAMPMEIER, M.D.

From the Departments of Urology and Anatomy, University of Illinois, College of Medicine, Chicago, Illinois

There are many theories which begin as logical deductions, and later without foundation of observation are handed down from textbook to textbook and from paper to paper as facts. Such a one is the hypothesis of the origin of cystic kidney. When the embryologists discovered that the ureter, renal pelvis, and the collecting ducts of the kidney, on the one hand, and the uriniferous tubules of its cortex, on the other, spring from two different sources, the former as an outgrowth of the caudal end of the mesonephric or Wolffian duct, and the latter from the mesenchymal nephrogenic blastema into which the ureteric bud grows and sprouts, and that as the uriniferous tubules "crystallize" and take form in the blastema they unite with the developing collecting ducts, what was simpler and more logical than to assume that occasionally such union may fail to occur and that the uriniferous tubules continuing their functional differentiation swell out more and more with their secretions. Though the writer cannot present observations to disprove this possibility, he has perused the literature in vain for a statement of established evidence. On the contrary, he has shown (1923-1924) that some of the early generations of uriniferous tubules joining normally the corresponding collecting ducts break away from them again and undergo cystic degeneration during the later developmental stages of the kidney. This phenomenon is not a sporadic one; every human being passed through such a phase during his embryonic life and it is no less characteristic than the physiologic umbilical hernia, for example, which is transitory during embryonic existence.

During the remaining few minutes an attempt will be made to review as simply and concisely as possible the evidence from an extensive investigation of an involved subject.

It has long been known that some twelve or more orders or generations of collecting tubules are established by repeated branch-

ing and rebranching of the primary outgrowths from the primitive ureteric bud. It is also well known that the nephrogenic blastema which originally caps the ureteric bud becomes divided and subdivided into smaller masses from which form the individual urinif-

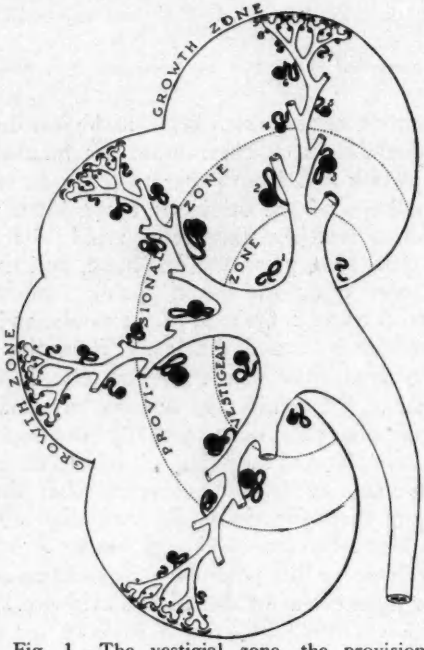

Fig. 1. The vestigial zone, the provisional zone, the growth zone.

erous tubules that early establish connection with the corresponding branches or generations of collecting tubules. It is generally stated that the first uriniferous tubules to be formed belong to the fourth or fifth generation of collecting ducts—in other words, that the first three or four generations of collecting ducts are devoid of such tubules. Doubtlessly, this belief arose when it was found that the first few generations of collecting ducts widened and became incorporated in the expanding renal pelvis to form its calices; for if such is the case, why should there be uriniferous tubules belonging to them? The seeming correctness of this conclusion was

supported by the knowledge that no uriniferous tubules open directly into renal pelvis or calices.

The writer has shown the error of such conclusions. The actual sequence of events is indicated by a relatively simple diagram (Fig. 1), constructed after an intensive study of serial sections of kidneys of many human embryos and fetuses of different ages. Here it is clearly pointed out that there are uriniferous tubules for

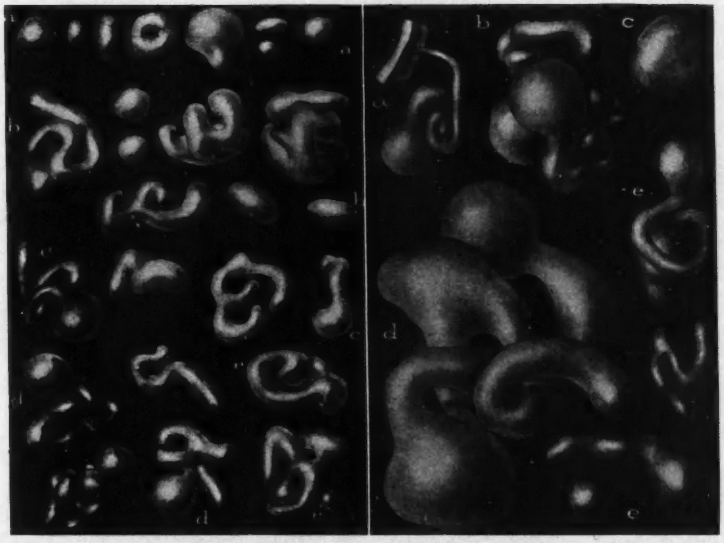

Fig. 2. The reconstructions of tubules in the vestigial generation.

every generation of collecting ducts—in other words, that already when the first collecting ducts sprout from the primitive renal pelvis, a corresponding generation of uriniferous tubules emerge from the surrounding nephrogenic blastema. These tubules, the first to appear, lie adjacent to the renal pelvis, as depicted in the diagram, and differ from all succeeding generations of tubules in that they are vestigial from the beginning. They generally appear stunted and misshapen, many possess no glomerulus, they rarely join the neighboring primary collecting ducts, and except infrequently, disappear later without leaving a trace. Because of their

character, the writer has termed the area immediately around the pelvis of the embryonic kidney in which they lie as the "vestigeal zone" (Fig. 1).

The next two or three tiers or generations of uriniferous tubules (Fig. 1), corresponding to the second to the fourth branchings of the collecting ducts, become normally established, possess well-formed coils and glomeruli, and early unite with the collecting ducts. After a short period they separate from them. Some of

Fig. 3. Cystic enlargements.

them expand cystically to several times their original size, and then usually collapse and disappear. These events precede, or are synchronous with, the widening of the collecting ducts for their incorporation into the expanding renal pelvis. Accordingly, the writer has called this zone of the developing kidney the "provisional zone" of uriniferous tubules (Fig. 1).

The third or outermost zone of the developing kidney may be termed the "growth zone," for here is established the definitive cortex (Fig. 1). Here, all uriniferous tubules, which are developed in association with the higher orders of collecting ducts, persist as normally functioning tubules throughout life.

Returning again to the forms which the early or doomed generations of uriniferous tubules take, we may refer first to Figure 2,

which illustrates reconstructions of different tubules of the first or vestigeal generation. Note their great diversity in shape and size, unmistakable signs of their degenerative character. Sometimes these regressive tubules may undergo cystic enlargement, as shown in Figure 3, particularly by tubule *d*.

Of the next two or three tiers or generations of uriniferous tubules, that is, those of the provisional zone, many are subject to

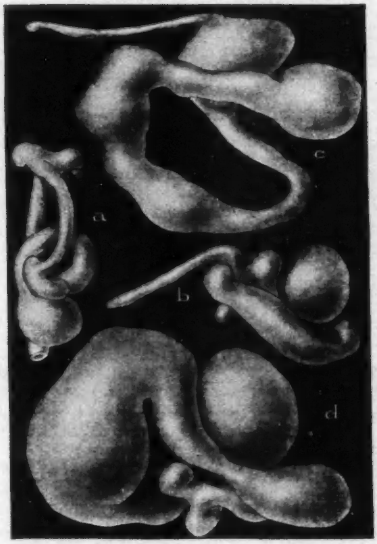

Fig. 4. A further cystic condition of the tubules.

cystic degeneration. In Figure 4 a reconstruction of a tubule *(a)*, when it is still joined to its collecting duct, should be compared with its condition *(d)* after it has broken loose from it. In section (Fig. 3) the cystic condition of such tubules is even more striking *(T. II*)*, when contrasted with the tubules of normal size in the vicinity. Generally, these cystic tubules will later collapse and vanish, but occasionally one or more may persist throughout life. Such have been traced throughout embryonic and later fetal life, as shown at *T. II**, and they occur in infants and in adults. Such

solitary cysts of the kidney are of variable size, from that of a small pea to that of a marble and greater.

If we have definitely established the genetic origin of solitary renal cysts, what can we say about the genesis of multiple cysts, that is, polycystic kidney. For this, the writer has been unable to secure a continuous chain of evidence. Should all tubules which have entered the initial phases in cystic formation continue to grow and distend at the same time, it is conceivable how the increasing pressure upon neighboring normal tubules would interfere with their normal genetic course and confluences, and accordingly subject a greater number of them to the same alteration until the entire or greater part of the kidney is affected.

Which factor controls the normal degeneration and suppression of redundant structures is obscure. That such a factor exists seems to be indicated by the fact that the abnormal growth of some structures which should normally disappear, or undergo reduction, or at any rate be passive, may not only occur in one but in several organs, as witnessed by the frequent association in the same individual of renal, hepatic, pancreatic, or genital cysts.

CASE REPORT

J. K., white, aged thirty-five years, an automobile service man, was admitted to Cook County Hospital, August 4, 1932, complaining of severe pain in the left side of his back and in the left side of his abdomen, and passing blood in the urine.

The patient stated that about eight hours before admittance to the hospital he had a scuffle and during the exercise was thrown across a bed. He stated that immediately upon being thrown across the bed he experienced severe pains in the left side of his back. This pain became increasingly severe as also did the pain in the left side of the abdomen. About two hours following the injury the patient stated that he noticed what he thought was blood in the urine. He had no other complaints. His past history, both medical and surgical, was negative.

Physical examination revealed a white male, fairly well nourished and fairly well developed who was apparently acutely ill and in extreme pain. Superficially there were numerous scratches and abrasions about the skin of the chest, arms, back and abdomen. The pupils were contracted, the conjunctivæ were very pale. The heart was not enlarged, the heart tones were of a fair quality, regular, and there were no murmurs or pericardial friction rubs. The lungs presented no abnormalities. The abdomen was distended. The entire left half of the abdomen was rigid. This was especially true of the

upper half; this area also presented a rounded, bulging area which was fairly firm upon palpation and extremely tender. No intra-abdominal organs were palpable.

There were no abnormal or pathologic reflexes elicited.

The radial arteries were soft and smooth, readily compressible, pulse 110, regular, fair volume and equal on both sides.

Blood pressure was 100/80 on both arms with the patient reclining.

The blood count revealed a 68 per cent hemoglobin, 4,000,000 red cells, 12,500 white cells and a coagulation time of 3.5 minutes.

The urine was acid, specific gravity 1.028, albumin 4 plus, sugar negative, microscopic field covered with red blood cells.

I saw the patient about six hours after admittance and made a tentative diagnosis of (a) probable extracapsular tear of the left kidney with reflex anuria, or (b) rupture of the left kidney. I advised that an intravenous pyelogram (skiodan) be made. This was done and the result was good.

Blood chemistry showed a urea nitrogen of 27.55 mgm. per 100 c.c. of blood. Creatinin was 2.1 mgm. per 100 c.c., and sugar 52.63 mgm.

The Kahn test was negative.

On August 5, 1932, the patient was operated upon and the left kidney was removed. The kidney upon being exposed was enveloped in a mass of dark red, clotted blood; the amount of blood was estimated at 500-600 c.c. Nephrectomy was carried out in the usual manner, two gauze drains were placed in the kidney fossa, and the wound was closed.

Grossly, this kidney was 24 x 10 x 11 cm. and almost completely converted into a mass composed of multilocular cysts, which ranged from the size of a common pin head to 3 cm. in diameter. There was practically no renal parenchyma intact. The cysts were filled with a clear fluid. The specimen also presented three recent lacerations, one in the upper pole of the kidney, one in the lower pole, and one in the region of the hilus. These lacerations varied from 1 cm. to 3 cm. in length, and the deepest one would admit one-half the length of the little finger.

Microscopically, the kidney was made up of multiple cysts which were lined by a single layer of epithelium. The intervening tissue was composed of compressed renal cortex and medulla.

Pathologic diagnosis was congenital polycystic kidney with recent lacerations.

Following the operation, the patient progressed satisfactorily until the thirteenth postoperative day when he developed a toxic psychosis from which he recovered. He was discharged as improved on September 9, 1932.

SURGICAL ASPECTS OF POLYCYSTIC KIDNEY

REPORT OF EIGHTY-FIVE SURGICAL CASES

WALTMAN WALTERS, M.D. (by invitation), and WILLIAM F. BRAASCH, M.D.

From the Division of Surgery and Section on Urology, The Mayo Clinic, Rochester, Minnesota

References to standard textbooks and other literature would indicate that there is uncertainty regarding the advisability of surgical treatment for polycystic kidney and that there are but few data available in regard to the results of treatment. This, we believe, is largely the result of too few cases having been studied to allow of definite conclusions being drawn. In one of the recent textbooks, reference is made to the report of Brin, in 1905, as follows: "Nephrectomy was carried out in seventeen cases—the mortality has been so high that this procedure stands condemned."

Our experience would seem to lead to a contrary opinion. A review of our records shows that some type of surgical procedure was performed at The Mayo Clinic on eighty-five patients who were found to have polycystic kidneys. Nephrectomy was performed in thirty-one cases. The Rovsing operation (puncture of cysts), or excision and drainage of the cysts, was carried out in twenty-nine cases, and exploration, either with or without an associated operation on some other abdominal viscus, was performed in twenty-five cases.

INDICATIONS FOR SURGICAL INTERFERENCE

Since most of the symptoms accompanying polycystic kidney are secondary to renal insufficiency or vascular disease, the majority of patients will present themselves to the internist rather than to the surgeon. However, with the onset of pain, hematuria, tumor, or secondary renal infection, the surgeon is usually consulted for relief.

The indications for surgical interference may be either primary or secondary. The primary factors are pain from distention of cysts and persistence of hematuria. Among the secondary complications are localized or diffuse renal infection, with pyonephrosis,

renal abscess, lithiasis, tuberculosis, and neoplasm. Surgical measures may be required for evacuation of cysts, in order to relieve intrarenal pressure and prevent further injury to the remaining renal tissue, as suggested by Rovsing.

In determining the advisability of operation from the standpoint of combined renal function, the peculiar conditions at hand present unusual problems. In the first place, as one of us has previously noted, lack of parallelism between the excretory and retention tests of renal function is often observed with polycystic kidneys. In other words, there is often marked delay and reduction in excretion of such dyes as indigocarmin and phenolsulphonphthalein, while the values for blood urea and creatinin may be normal or but slightly elevated. This may be explained in part by intrarenal anatomic conditions causing delayed excretion. The retention test, therefore, usually will be the more accurate index of renal function. If the value for urea is more than 50 to 60 mg. for each 100 c.c. of blood, the advisability of operation is open to question, except as an emergency measure, or when some temporary functional deterrent may be present, such as lithiasis or acute unilateral renal infection. In the light of our present experience, intravenous or excretory urography is a comparatively accurate index of renal function. Recognizable deformity will be visualized in fully two-thirds of the cases when the renal function will permit visualization. The details of the pelvic outline may be insufficient for interpretation, however, and the condition may not be recognized unless retrograde urography is employed. As a means of determining the comparative function of the two kidneys, intravenous urography will be of great practical value also. Adequate visualization of the pelvis of but one kidney can be regarded as sufficient evidence of normal renal function to warrant removal of the other kidney. In the interpretation of the intravenous urogram one should remember, however, that visualization of the renal pelvis may be absent or exceedingly dim with (1) idiosyncrasy on the part of the patient in excretion of iodine, (2) combined renal insufficiency as indicated by a value for urea of 60 mg. or more in each 100 c.c. of blood, and (3) some temporary reflex inhibition of renal excretion.

Pain.—In most of our series of eighty-five cases in which surgical procedures were carried out, a complaint of pain was made. It was usually referred to as a dull ache localized largely in the

lumbar region. In the presence of huge kidneys, pain may be caused by tension on the renal pedicle. Pain may also be caused by increase of intracystic pressure, particularly when the cysts are of extremely large size. In several cases one or two large cysts were present and their evacuation was followed by relief of pain. Intracystic hemorrhage, with resulting overdistention, may occur and may be the cause of renal pain. Pain may also occur as the result of ureteral obstruction by blood clots.

Hemorrhage.—In a recent review of clinical data concerning 193 patients with polycystic kidney observed at the clinic, it was found that gross hematuria occurred in 30 per cent. The combination of hematuria with a tumor felt in a lateral upper abdominal quadrant is usually so suggestive of neoplasm that surgical exploration and even nephrectomy have frequently been reported before the true condition was recognized. In most cases the hematuria is moderate and continues only a few days. Intracystic hemorrhage probably occurs often with polycystic kidney, without hematuria. On cross section of the kidney, cysts are often found, containing dark colored material, which very evidently represents the residue of a previous hemorrhage. If intracystic hemorrhage is very slight or intermittent, neither pain nor hematuria may occur. However, if the hemorrhage is continuous, the cysts either become distended and cause severe pain, or they may rupture into the renal pelvis with resulting hematuria. If the hematuria is excessive or long continued, surgical interference may be indicated. Evacuation and drainage of these cysts, particularly when large, may suffice. Should there be evidence of secondary widespread renal destruction, nephrectomy may be necessary. Incidentally, it should be remembered that hematuria with polycystic kidneys does not necessarily signify its renal origin. Coincident bleeding from other parts of the urinary tract often has been observed, and their exclusion from consideration, by means of cystoscopy, usually is necessary.

Renal Infection.—Urinalysis will disclose the presence of a small amount of pus in the majority of cases of polycystic kidney. Many patients will complain occasionally of intermittent frequency of micturition or of dysuria. As the cysts become distended and project into the lumen of the calices, they can readily cause inadequate drainage of the urine with secondary infection. It is surprising

that infection which requires surgical treatment does not occur more frequently in these kidneys. Such infection is usually found in one kidney only, suggesting its anatomic origin. Widespread renal infection may have a most insidious onset and may not give rise to acute symptoms until the renal tissue is largely destroyed. Infection of intracystic origin, confined to one or more adjacent cysts, is often observed. Perinephritic abscess, having its origin in infected cysts, may occur. Stone is occasionally found with polycystic kidney, and probably occurs secondary to insufficient drainage of a calix. Calculi were found in five of the eighty-five cases and were accompanied by so much infection that nephrectomy was necessary. Chemical examination revealed that they were composed largely of calcium phosphate and were probably found as a result of inadequate renal drainage.

INCISION, EXCISION AND ENUCLEATION OF THE CYSTS

Incision, excision and enucleation of cysts are used to accomplish relief of pain caused either by pressure of the polycystic mass on adjacent structures or by intracystic distention. When the cysts are of moderate size, the use of multiple punctures, as suggested by Rovsing, is the preferable procedure. This may be combined with excision or enucleation of larger cysts which may be accessible to such procedures. With infection present within the cysts, unless complete drainage of the perirenal region is established, the infection may extend into the remaining renal as well as perirenal tissues, and nephrectomy will be required. For this reason, operations of this type should not be undertaken unless one is certain that the function of the opposite kidney is capable of sustaining life. The results of incision, excision and enucleation of cysts of polycystic kidneys are variable. Rovsing reported several cases in which remarkable amelioration of pain occurred subsequent to multiple puncture; in addition, the renal function was considerably improved. Other surgeons have confirmed these results in some cases, whereas others have reported failures, and have found that secondary nephrectomy became necessary later. Brin reviewed sixteen cases treated by incision of cysts, and stated that there was a mortality rate of 25 per cent in this series, and that results among patients who lived were uncertain.

In our series there were twenty-four cases in which the Rovsing

operation, or puncture of multiple cysts, was performed, and five additional cases in which cysts were removed or enucleated. There were four deaths in hospital from uremia, perirenal and retroperitoneal bleeding, and infection; this gives a mortality of 13.8 per cent. Thirteen of these patients are living and in fairly good health at the present time, after periods varying from three to twenty-one years following operation. Subsequent deaths occurred in seven cases, in periods varying from one to seventeen years (Table I).

TABLE I. ROVSING OPERATION AND REMOVAL OF CYSTS

	Patients	Deaths in Hospital
Rovsing operation	24	4 (16.6 per cent)
Removal or enucleation of cysts	5	
Total	29	4 (13.8 per cent)

Survived operation (25 cases)

Patients now living	13
2 less than 3 years	
11 from 8 to 21 years	
Patients now dead	7
1 lived more than 10 years	
3 lived 5 to 10 years	
2 lived 3 to 5 years	
1 lived less than 3 years	
Not traced	5

NEPHRECTOMY

Nephrectomy was indicated and performed in thirty-one cases. There was but one death as the result of this operation; the patient was a man, sixty-seven years of age, whose removed kidney also contained an adenocarcinoma graded 3. The youngest patient was aged twenty-one months, and the oldest, sixty-nine years. Nephrectomy was performed for the most part because of advanced renal infection associated with marked reduction or destruction of renal function. Included in this group were five patients with calculi and three with malignant disease. In three of the cases, nephrectomy was performed as a secondary procedure subsequent to puncture of cysts (Rovsing operation). Eighteen patients of this group are living at the present time, from one to nineteen years after operation. Particular attention is directed to a patient, forty-three years of age at the time of nephrectomy, who has reported

his condition as being excellent nineteen years subsequent to nephrectomy. A patient, who was twenty-one months of age at the time of the nephrectomy, has been in good health during a period of fourteen years and four months (Table II).

TABLE II. RESULTS FOLLOWING PRIMARY NEPHRECTOMY FOR POLYCYSTIC KIDNEY (28 CASES)

	Patients	Per cent
Now living	18	64.2
1 after 19 years		
4 from 13 to 19 years		
3 from 7 to 13 years		
3 from 4 to 7 years		
7 from 8 months to 4 years		
Dead	5	17.85
2 lived from 9 to 13 years		
2 died within 3 years		
1 died in hospital		
Not traced	5	17.85
Nephrectomy was performed secondary to Rovsing operation in 3 additional cases.		
Total number of nephrectomies	31	
1 patient died in hospital, mortality	3.2 per cent	

Practically all of these patients who have lived more than a year have reported their condition to be good or excellent, with the following exceptions: After a period of nine years, one patient reported some pain in the opposite renal region; another, after seven years, reported enlargement of the remaining kidney and hematuria; another reported hematuria and dysuria one year and seven months subsequent to nephrectomy. Three patients who were subjected to nephrectomy secondary to the Rovsing operation died subsequently; one after eight years, one after six years and five months, and one after two months. In all three cases death was due to uremia.

SURGICAL EXPLORATION

Explorations of polycystic kidneys, without other surgical procedures on them, were carried out in twenty-five cases. In eleven of these cases intra-abdominal operative procedures were carried out for lesions of one or another of the intra-abdominal viscera, and the presence of polycystic kidneys was an accidental finding. The discovery of polycystic kidneys in the course of abdominal operations in so large a number of cases is suggestive of clinical

negligence. However, many of these patients were operated on before methods of diagnosis were as accurate as they are at present. Furthermore, it is surprising how often bilateral renal enlargement is not detected in abdominal palpation. Owing to the great difference in degree of involvement which often occurs, frequently only one kidney is found enlarged on palpation. This may account for the erroneous clinical diagnosis of renal neoplasm which is often made, and with possible disastrous results, if nephrectomy follows. With the aid of modern methods of diagnosis and par-

TABLE III. EXPLORATIONS FOR POLYCYSTIC KIDNEYS

Patients	Died in hospital	Mortality, per cent	Now living	Now dead	Not traced
14	1	7.1	6	6	1
Polycystic kidneys accidentally found at time of other intra-abdominal operations					
11	0		5	6	

ticularly with the more general employment of intravenous urography, attention should usually be called to the condition present, even if other clinical data fail.

Coincident cysts in the pancreas, liver, and other organs, which might confuse the clinical picture, are often found in the course of abdominal exploration. These cysts are usually confined to a limited region, usually are not progressive in size or number, and do not seem to affect the function of the organs involved. They may occasionally become very large; in one case in which we performed exploration, a cyst of the liver was found to be of such size as to cause caudad displacement of the kidney to the level of the crest of the ilium. Occasionally large cysts are found in the liver and in other organs, without renal involvement.

Major surgical procedures were carried out in this group of cases, for cholelithiasis, uterine fibromas, duodenal ulcer, and appendicitis, and in one case colostomy was performed for carcinoma of the rectum. None of the patients died subsequently, over periods of from one to ten years. Five patients of the group are living,

for periods varying from six to ten years; two of them are in good condition (Table III).

It would seem, therefore, that intra-abdominal surgical operations can be carried out in the presence of polycystic kidney without appreciable increased risk, providing combined renal function is within normal limits.

SUMMARY AND CONCLUSIONS

The contention that surgical treatment of polycystic kidney is seldom, if ever, indicated is erroneous. Complications with polycystic kidney, which require surgical treatment, occur frequently. The estimation of renal function is of fundamental importance in determining the prognosis and the advisability of operation. Owing to the anatomic conditions present in the polycystic kidney, retention tests of renal function usually give a better index than the excretory tests.

Evidence of marked disturbance of function of both kidneys such as is indicated by a value for urea of 50 to 60 mg. or more for each 100 c.c. of blood, usually will contra-indicate surgical treatment except as an emergency measure. When complications exist in one kidney which would indicate nephrectomy, it is essential first to determine whether the degree of function of the other kidney is sufficient to sustain life. Bilateral renal deformity visualized by intravenous or excretory urography, should serve in many cases to call attention to the possibility of polycystic disease. It should also serve to make evident the comparative degree of function in either kidney and so govern the type and the advisability of operation. A polycystic kidney in which a clinical diagnosis of renal tumor had been made has been removed not infrequently. The most common complication requiring surgical treatment occurring with polycystic kidney is diffuse or localized infection. Diffuse, subacute renal infection may have an insidious onset, and there may be but few localizing symptoms. Renal pain is a common symptom and is usually described as a dull ache, although it may become acute. It may be caused either by excessive renal weight exerting a pull on the renal pedicle, by intracystic or external pressure, or by infection. Puncture or enucleation of one or more large cysts may serve to ameliorate or eradicate pain. Hematuria, usually of moderate degree and limited duration, may become

copious and long continued. Such hematuria is usually the result of intracystic hemorrhage with rupture of the cyst into the renal pelvis. Excision or enucleation of such cysts usually will suffice to control the hemorrhage. Should destruction of the kidney be extensive, or accompanied by secondary infection, nephrectomy may be necessary. Other complications observed with polycystic kidney are renal calculus, neoplasm, tuberculosis and hydronephrosis. The value of the Rovsing operation, which was conceived for the purpose of removing pressure by the cysts on the remaining renal parenchyma, still remains undetermined. Theoretically it has much in its favor. Unfortunately, secondary infection or a persistent urinary fistula may develop following the operation, necessitating nephrectomy. If such complications could be obviated, the procedure might well merit further consideration. It is difficult to evaluate the results obtained in the few cases in which the Rovsing operation was successfully carried out. Although many lived for a long time after operation, this is equally true in cases in which surgical treatment was not employed.

DISCUSSION

DR. GUY L. HUNNER (Baltimore, Md.): I am sorry that I arrived in the midst of Dr. Braasch's paper and did not hear all of it. He may have mentioned the point which I wish to bring up, and that is the relationship of ureteral stricture to some of these cases.

We all know how surprised we are over the apparent good health many of these patients have enjoyed in spite of their condition being a congenital one, and in spite of the small amount of good kidney substance that can be left, as shown by our various functional and clinical examinations, or as shown by direct inspection when we stumble into the correct diagnosis at operation. I have found that apparently some of these patients have recently begun to fail in health rather rapidly and come to the urologist because of symptoms due to the more or less recent shutting down of ureteral stricture areas.

Dr. Braasch mentioned the hydronephrosis, the chronic infection, and the stones present in some of these cases, and he ascribes those conditions, as I understood him, to the presence of the polycystic condition in the kidney causing more or less interference with the drainage. I feel sure that in many of them the real cause of the bad drainage and of these secondary conditions is ureteral stricture.

If we accept the idea, as I suppose we all do, that these are congenital malformations, it would only be natural to think that there might be the congenital stricture in some of them. Some of the strictures, I fully believe from experience, are secondary to some focal infection, and we have to take care of the infection areas while we take care of drainage.

I think we all feel the futility of trying to relieve these patients by any form of operation, so we ought to be very thankful if there is anything as simple in their treatment as restoration of good ureteral drainage, and some of them have gone along for a number of years in astonishingly good health after having their ureteral drainage attended to.

I might say that I don't think the passage of a five or six or

seven catheter without any obstruction tells you that the patient has no ureteral stricture. If you don't believe in using the bulb to find out whether they have stricture, I would at least recommend that you pass very large catheters or dilating bougies merely as an empiric method in these cases, because a certain goodly percentage of them do have strictures, and you will get results, no matter what method you use, if you get the better drainage.

DR. F. R. HAGNER (Washington, D. C.): I did not notice that the gentlemen mentioned any congenital cases. I would like to report a case of Dr. Morse of this city in a child at birth, which I saw. This tumor was so large that it interfered with the delivery of the child. The specimen now is in the Army Medical Museum. The kidney was about ten times the normal size. I do not know whether the child died immediately after birth, but it either died at birth or immediately afterwards.

As regards the condition of the opposite kidney, I am not sure, as it has been a good many years ago. This was a typical polycystic kidney, only smaller, of course, than is seen in adults.

DR. ALEXANDER RANDALL (Philadelphia, Pa.): I experienced this past winter the demonstration of a clinical observation, or the interpretation of a clinical study, which to me was new, in differentiating polycystic disease from other lesions.

A man of sixty-odd was admitted to the medical service for a cardiac condition, a peripheral edema and a pyodermia. I was asked to see him because in the examination those in the medical service had been able to make out a mass in either loin space. The patient was fairly stout and his prostate on palpation was typically hypertrophied. He was found to have a large residual urine of over 300 c.c. and pyuria. There were palpable masses in either loin. We had studies by intravenous urography which showed very marked dilatation of the pelves, nothing characteristic of anything more than a bilateral back pressure hydronephrosis. We advised his transfer to the urological service for what we took to be a rather characteristic and typical picture of an obstructed uropathy arising fom the prostate. It became interesting because the medical side of the house split. Dr. Pfeffer stood by me, that the man had back pressure hydronephrosis and the masses felt were large hydronephrotic kidneys. On the other hand, the Professor of

Medicine, Dr. Stengel, with his associate, Dr. Fitzhugh, had made a diagnosis of polycystic kidneys. We weren't really anxious for the man and his clinical condition was not good for surgery, so the argument was continued.

That man's kidney function was the interesting point. The blood urea nitrogen was not elevated unduly, somewhere in the twenties or thirties, but his phthalein output was remarkably low. He died and an autopsy was performed. The two attacking parties met at the mortuary, and Dr. Pfeffer and I took a "licking." The patient had bilateral polycystic kidneys.

The argument, as I say, had gone on for some time pro and con. When it was demonstrated, Dr. Pfeffer took Dr. Stengel aside and said, "How did you know it?" Then it was that he unveiled this clinical interpretation of the evidence and brought out a point that I have not heard mentioned before. He said, "If this man had an obstructive uropathy and bilateral hydronephrosis, such as you see in your prostatic cases so frequently, he should have had a high B.U.N., because that is a progressive destructive process and with that goes the blood picture of gradually destroyed renal function, but the polycystic man travels on his plane over an indefinite period of time, and, as we know, reaches elder years in fair renal balance, but when he cracks, he cracks abruptly, suddenly, and dies almost before his B.U.N. has a chance to go up."

I thought it was a very practical interpretation of those clinical tests, and I hadn't seen it brought out before.

Dr. Charles M. McKenna (Chicago, Ill.): I was glad to hear what Dr. Braasch had to say regarding infection. I know of no operation where the surgeon requires more careful technic so as to guard against infection than he does in the operation on polycystic kidney. Dr. Hagner presented a case of polycystic kidney in the new-born. You know in a great many of our textbooks, polycystic kidney is not mentioned in the new-born. We have one in our museum in the College of Medicine, University of Illinois.

Inasmuch as Dr. Hunner spoke about ureteral stricture, I should like to make a few remarks concerning the management of the ureteral stump after nephrectomy. It is particularly valuable in patients suffering with renal tuberculosis. I think we have all experienced difficulty in having the wound close in that class of case where we are dealing with a tuberculosis or even the ordinary

hydro-ureter. In those cases the urine backs from the bladder up the ureter and continues to keep the fistula open.

We are using two simple methods for that:

In one method we introduce a ureteral catheter into the kidney before operation all the way to the pelvis of the kidney, and before cutting the ureter, strip the ureter down as far as possible. Then when the ureter is cut it can be tied to the distal end of the catheter with just the tip of the catheter protruding above the cut edge of ureter. Next have the assistant withdraw the catheter through the penis which in turn will invaginate the ureter down as far as the operator believes it necessary; in fact, one can draw it into the bladder and remove it through the suprapubic opening. This, I think, would be rarely indicated; in other words, the ureter is turned outside in.

The other method is simply tying off the ureter after it has been severed from the kidney and invaginating it and managing it the same way as you do the cut off end of the appendix in doing an appendectomy. In simple cases, the invagination need not be more than 1 or 2 inches. A ligature will then tie off the ureter twice and do away with an open surface.

Dr. William F. Braasch (Rochester, Minn.): I was very much interested in the pyelogram that Dr. McKenna showed in which you recall the pelvic outline of the opposite kidney was apparently normal. This occurs every now and then and is one of the causes for error in diagnosis.

I formerly thought that polycystic kidney without visible deformity in both renal pelves was impossible, but in recent years I have seen several cases where it was impossible to determine any deformity in the pelvis of the kidney, or changes so slight that no positive interpretation of deformity could be made. The progress of polycystic disease may be unequal. Its progress may be very slow on one side and rapid on the other.